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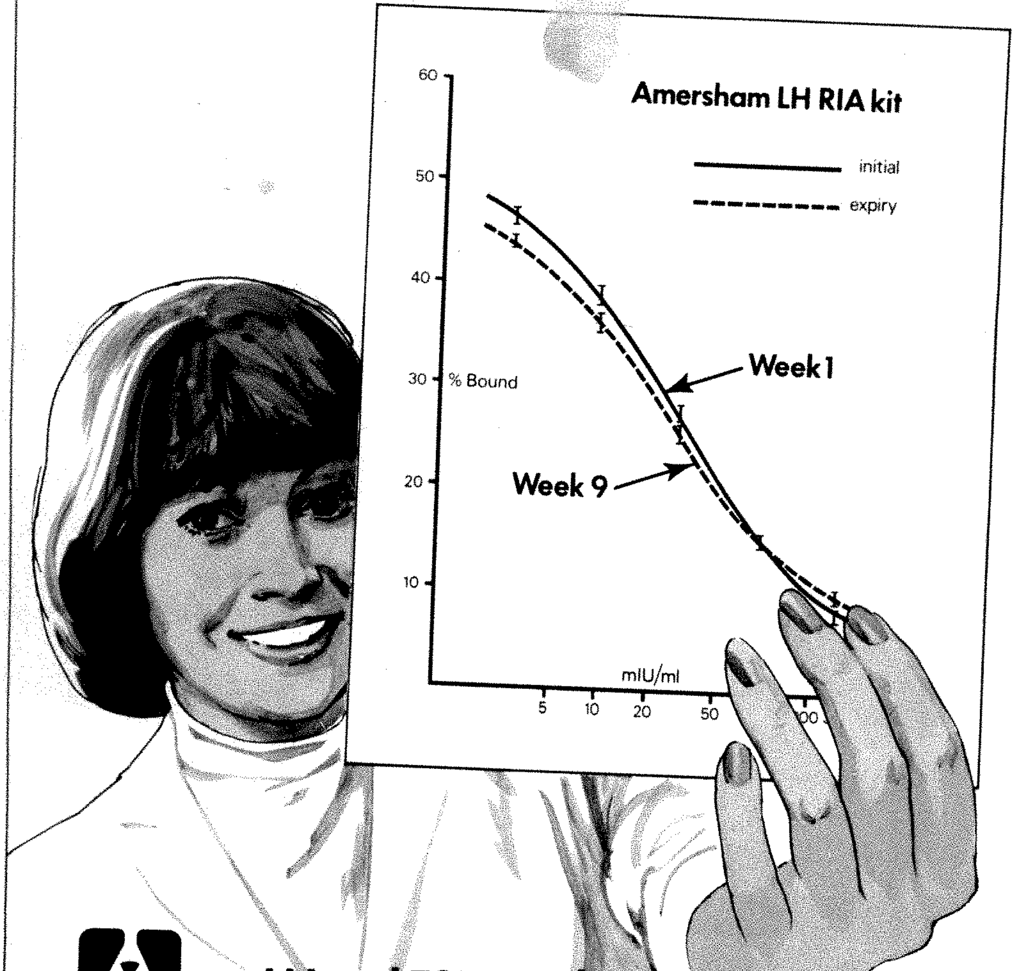

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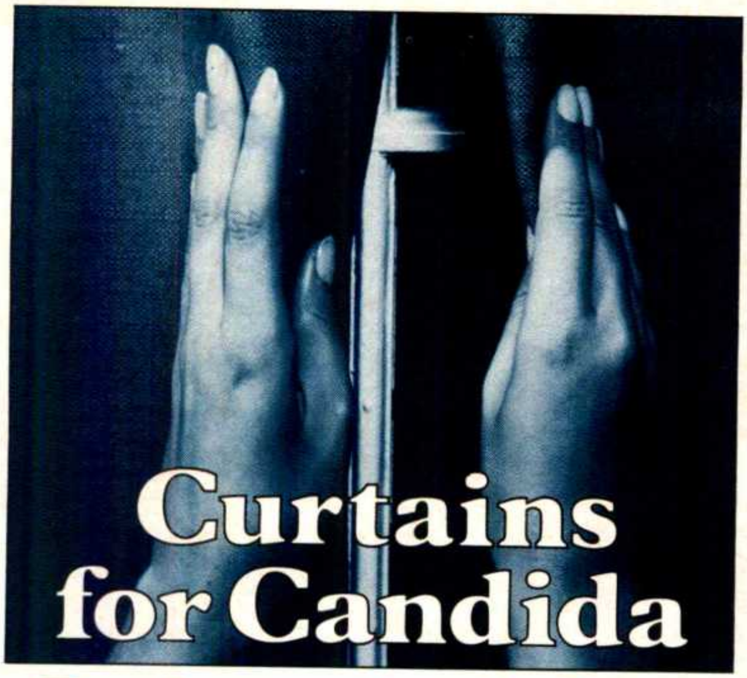

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CONTRA-INDICATIONS, WARNINGS, etc.

Contra-indications None known.

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PACKAGE QUANTITIES Packs of three pessaries with applicator.

Price – 3 pessaries with applicator £3.60

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References

1. Avram, A. et Grupper, Ch. Bulletin de la Société Française de Mycologie Médicale 1975 Tome IV (2).
2. Preusser, H.J. et al. Research Report 1974. On file Cilag-Chemie.
3. Schweisfurth, R. Research Report 1974. On file Cilag-Chemie.

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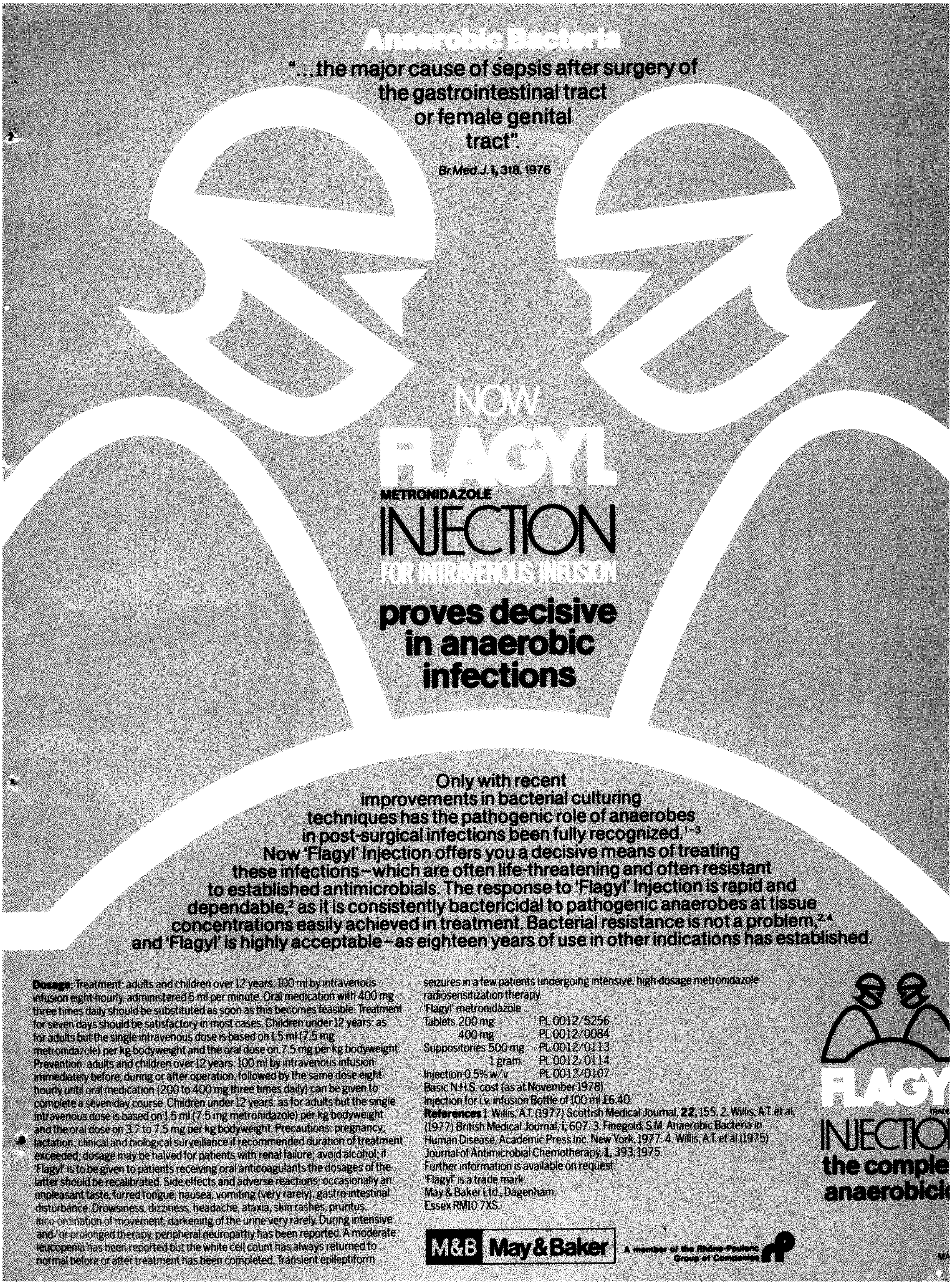
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References 1. Willis, A.T. (1977) Scottish Medical Journal, **22**, 155. 2. Willis, A.T. et al. (1977) British Medical Journal, **i**, 607. 3. Finegold, S.M. Anaerobic Bacteria in Human Disease, Academic Press Inc. New York, 1977. 4. Willis, A.T. et al (1975) Journal of Antimicrobial Chemotherapy, **1**, 393, 1975.

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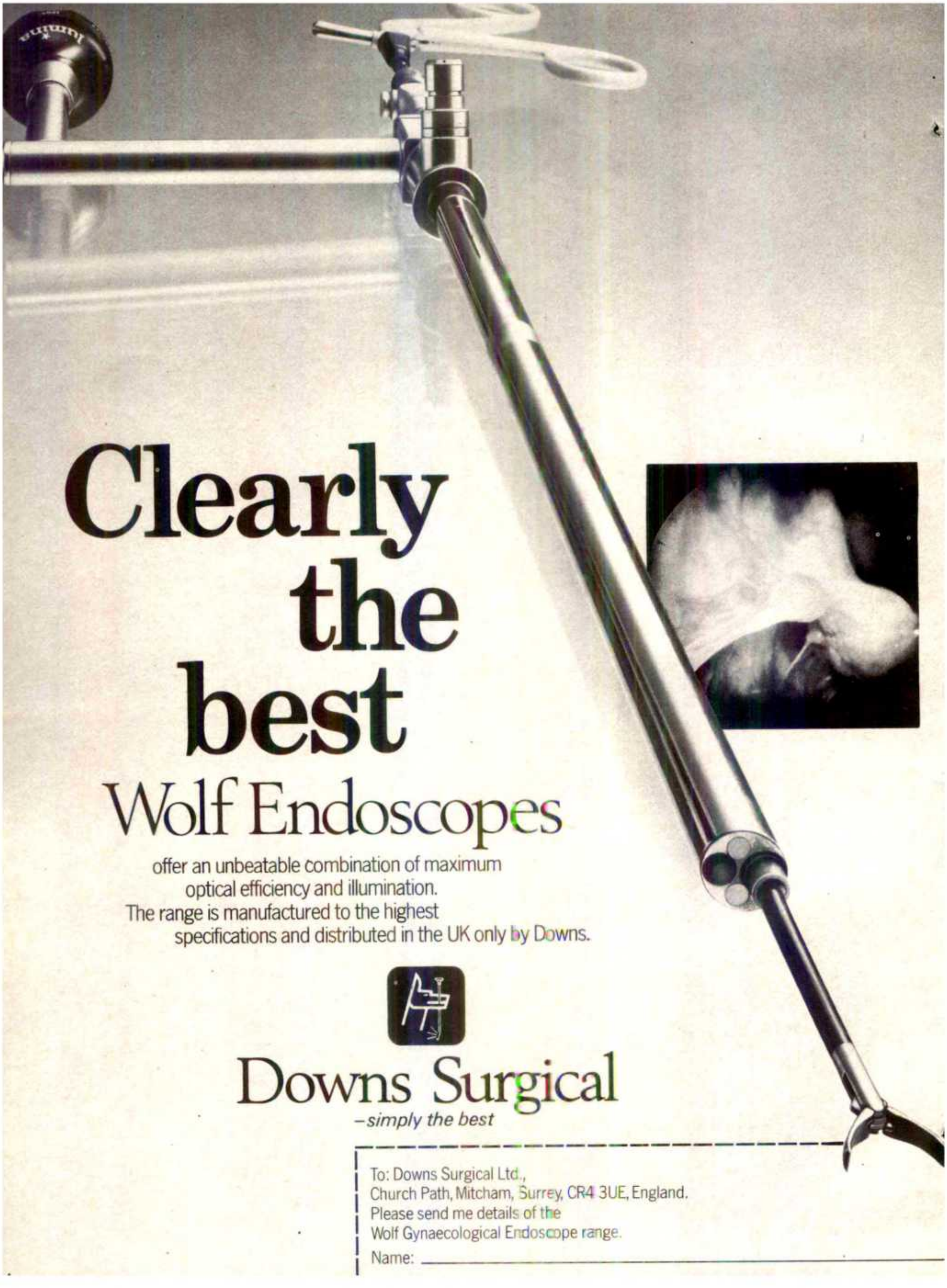

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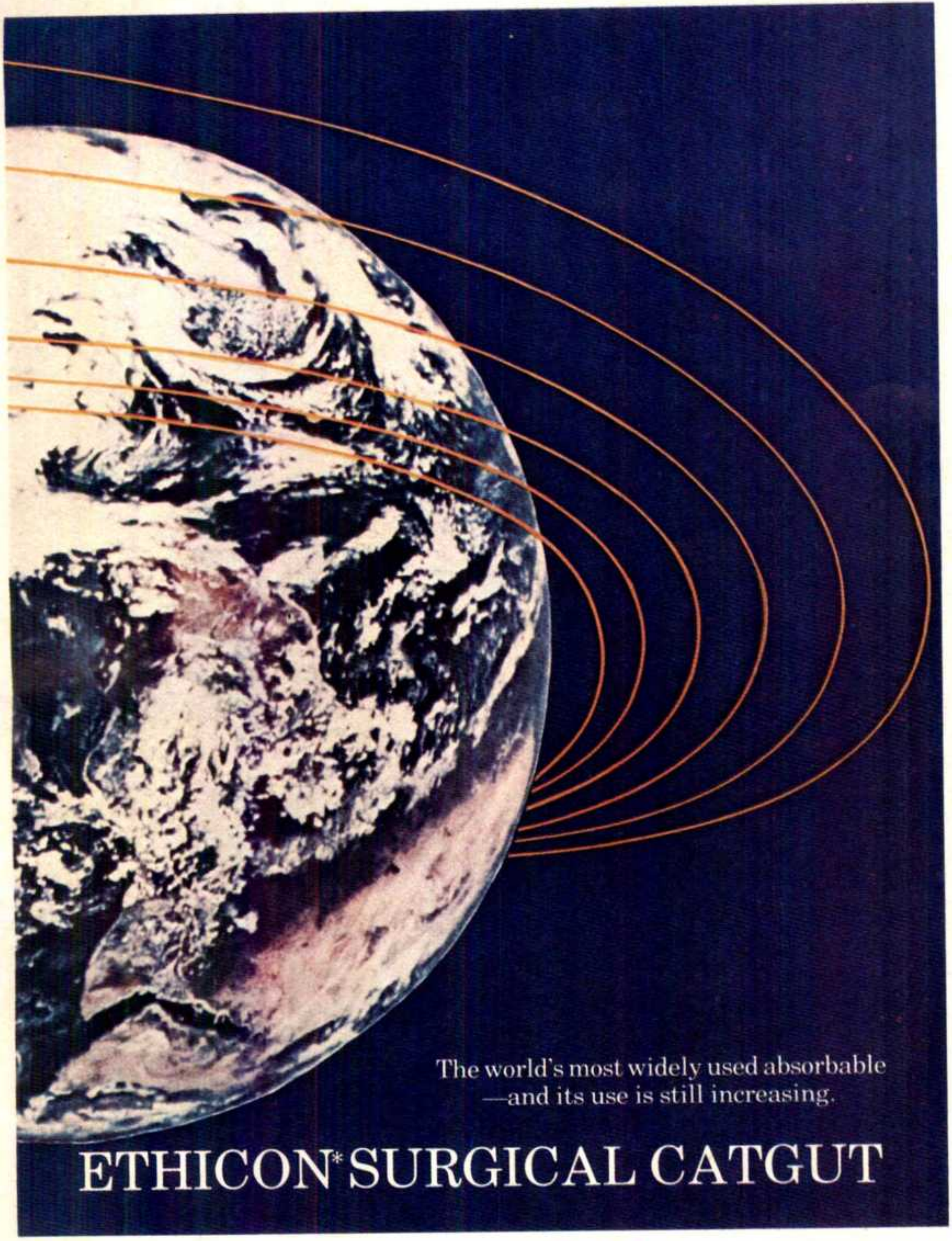
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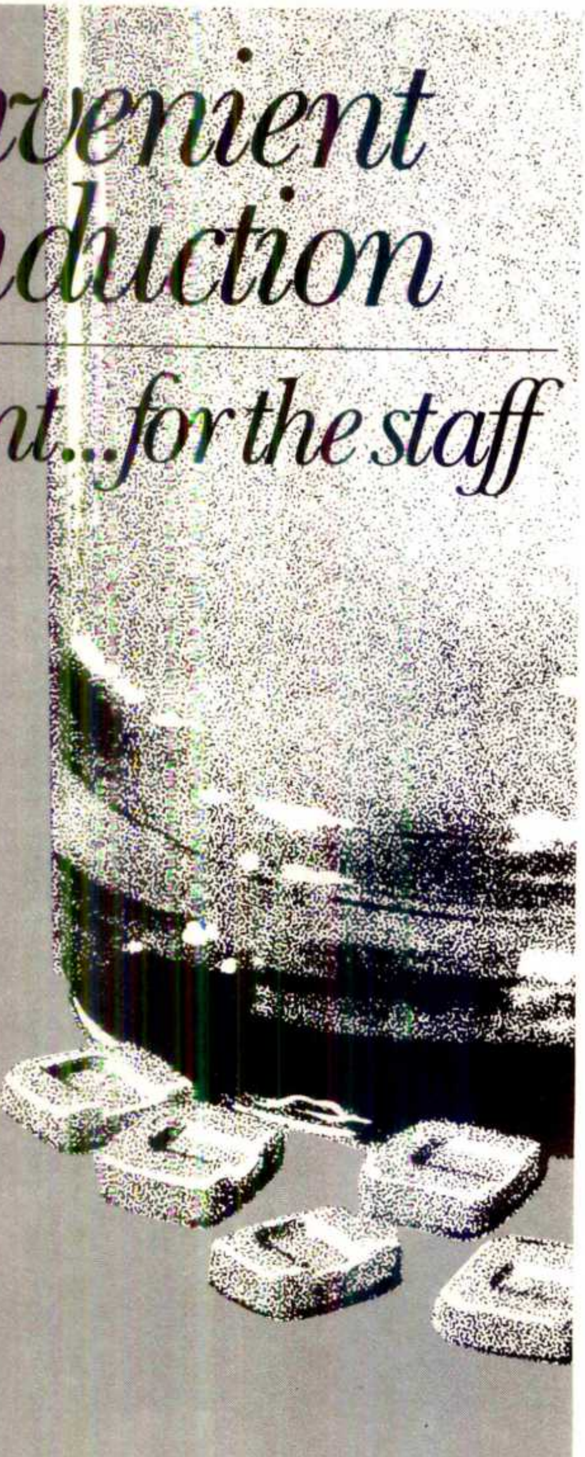

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Contra-indications, Warnings etc.
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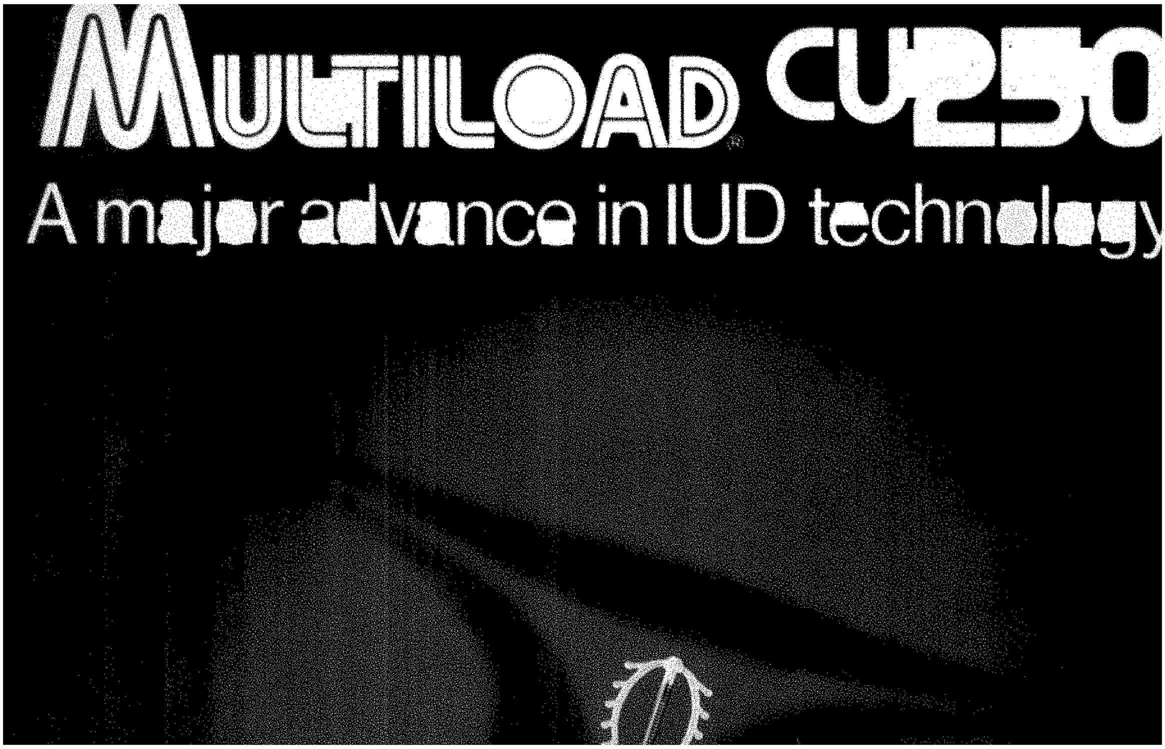
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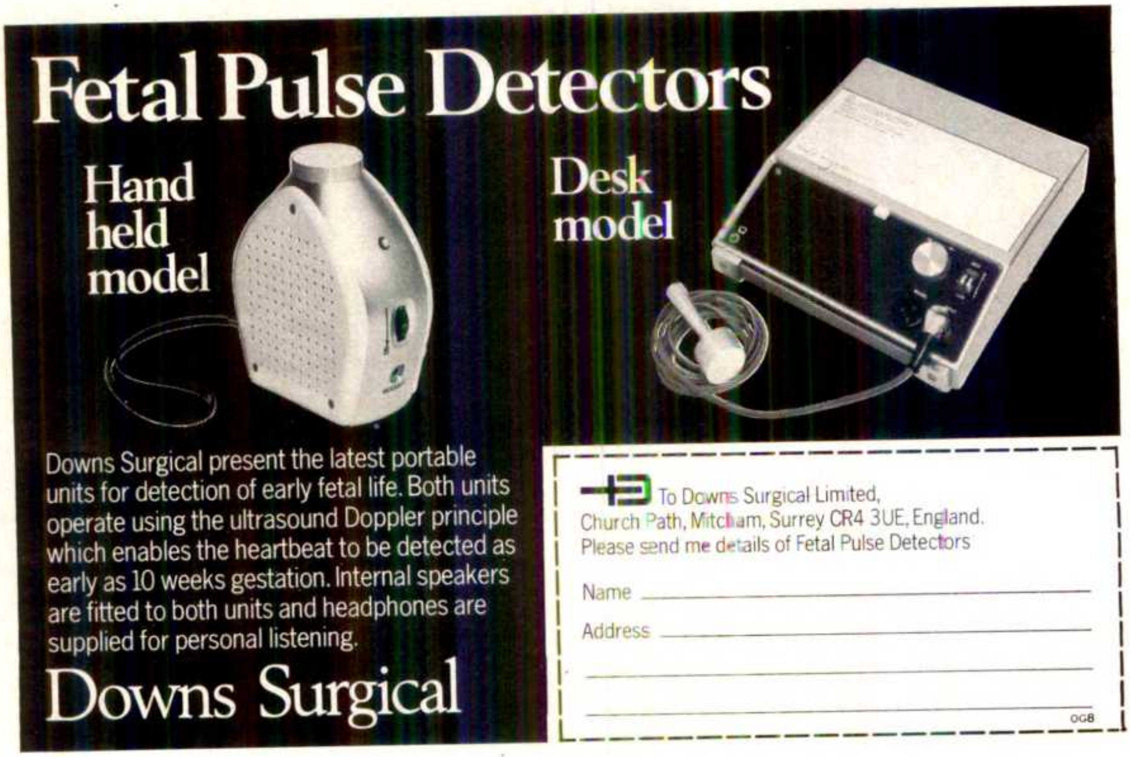

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1. J. int. med. Res. (1977) 5 (Suppl. 3): 86-91.
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A repeat course of cisplatin should not be given until the serum creatinine is below 1.5 mg/100 ml (130 μmol/l) and/or the blood urea below 55 mg/100 ml (9 mmol/l). A repeat course should not be given until circulating blood elements are at an acceptable level (platelets 100,000/mm^3, WBC 4,000/mm^3). Subsequent doses of cisplatin should not be given until an audiometric analysis indicates that auditory acuity is within normal limits. When employed in combination with other antitumour drugs, the dose of cisplatin should be adjusted appropriately.

CONTRA-INDICATIONS, WARNINGS, ETC.

Cisplatin induces nephrotoxicity, myelosuppression and ototoxicity which may be additive to pre-existing dysfunctions. Consequently, the use of cisplatin in patients with hearing or renal impairment or depressed bone marrow function may be associated with increased toxicities. Such conditions represent relative contra-indications.
Cisplatin is contra-indicated in patients with a history of hypersensitivity to cisplatin or other platinum-containing compounds.

WARNINGS

Cisplatin produces cumulative nephrotoxicity. The serum creatinine, BUN and creatinine clearance should be measured prior to initiating therapy, and prior to each subsequent course.
Anaphylactic-like reactions to cisplatin have been reported. These reactions have occurred within minutes of administration to patients with prior exposure to cisplatin, and have been alleviated by administration of adrenaline, steroids and antihistamines.
Safe use in pregnancy has not been established. This product should not normally be administered to patients who are pregnant or to mothers who are breast feeding. Cisplatin is mutagenic in bacteria and produces chromosome aberrations in animal cells in tissue culture. Although carcinogenicity and teratogenicity have not been established, compounds with similar mechanisms of action and mutagenicity have been reported to be carcinogenic.
The influence of cisplatin on human reproduction has not been determined. Cisplatin therapy might have an antifertility effect.

Precautions

Cisplatin should be administered by individuals experienced in the use of antineoplastic therapy.
Since renal toxicity is cumulative, measurements of BUN, serum creatinine and creatinine clearance should be performed prior to initiating therapy and prior to each subsequent dose. At the recommended dosage, cisplatin should not be given more frequently than once every 3 to 4 weeks. (See Adverse Reactions).
Since ototoxicity of cisplatin is cumulative, audiometric testing should be performed prior to initiating therapy and prior to each subsequent dose of drug. (See Adverse Reactions).
Peripheral blood counts should be monitored weekly. Liver function should be monitored periodically. Neurological examination should also be performed regularly. (See Adverse Reactions).

ADVERSE REACTIONS

Nephrotoxicity

Dose-related and cumulative renal insufficiency is the major dose-limiting toxicity of cisplatin. Renal toxicity has been noted in 28 to 36% of patients treated with a single dose of 50 mg/m^2. It is first noted during the second week after a dose and is manifested by elevations in BUN and serum creatinine, serum uric acid and/or a decrease in creatinine clearance.
Renal toxicity, becomes more prolonged and severe with repeated courses of the drug. Renal function must return to normal before another dose of cisplatin can be given.
Renal function impairment has been associated with renal tubular damage. The administration of cisplatin using a 6-8 hour infusion with intravenous hydration and mannitol has been used to reduce nephrotoxicity. However, renal toxicity still can occur after utilisation of these procedures.

Ototoxicity

Ototoxicity has been observed in up to 31% of patients treated with a single dose of cisplatin 50 mg/m^2, and is manifested by tinnitus and/or hearing loss in the high frequency range (4,000 to 8,000 Hz).
Decreased ability to hear normal conversational tones may occur occasionally. Ototoxic effects may be more severe in children receiving cisplatin. Hearing loss can be unilateral or bilateral and tends to become more frequent and severe with repeated doses. It is unclear whether cisplatin-induced ototoxicity is reversible. Careful monitoring of audiometry should be performed prior to initiation of therapy and prior to subsequent doses of cisplatin.

Haematological

Myelosuppression occurs in 25 to 30% of patients treated with cisplatin. The nadirs in circulating platelets and leucocytes occur between days 18 to 23 (range 7.5 to 45) with most patients recovering by day 39 (range 13 to 62). Leucopenia and thrombocytopenia are more pronounced at higher doses (50 mg/m^2). Anaemia (decrease in haemoglobin level by 2 g/100 ml blood) occurs at approximately the same frequency and with the same timing as leucopenia and thrombocytopenia.

Gastrointestinal

Marked nausea and vomiting occur in almost all patients treated with cisplatin, and are occasionally so severe that the drug must be discontinued. Nausea and vomiting usually begin within one to four hours after treatment and last up to 24 hours. Various degrees of nausea and anorexia may persist for up to one week after treatment.

OTHER TOXICITIES

Hyperuricaemia

Hyperuricaemia has been reported to occur at approximately the same frequency as the increases in BUN and serum creatinine. It is more pronounced after doses greater than 50 mg/m^2, and peak levels of uric acid generally occur between 3 to 5 days after the dose. Allopurinol therapy for hyperuricaemia effectively reduces uric acid levels.

Neurotoxicity

Neurotoxicity, usually characterised by peripheral neuropathies, has occurred in some patients. Loss of taste and seizures have also been reported. Neuropathies resulting from cisplatin treatment may occur after prolonged therapy (4 to 7 months). However, neurological symptoms have been reported to occur after a single dose.
Cisplatin therapy should be discontinued when the symptoms are first observed. Preliminary evidence suggests peripheral neuropathy may be irreversible in some patients.

Anaphylactic-like Reactions

Anaphylactic-like reactions, possibly secondary to cisplatin therapy, have been occasionally reported in patients previously exposed to cisplatin. The reactions consist of facial oedema, wheezing, tachycardia and hypotension within a few minutes of drug administration. All reactions may be controlled by intravenous adrenaline, corticosteroids or antihistamines. Patients receiving cisplatin should be observed carefully for possible anaphylactic-like reactions and supportive equipment and medication should be available to treat such complication.
Other toxicities reported to occur infrequently are cardiac abnormalities, anorexia and elevated SGOT.

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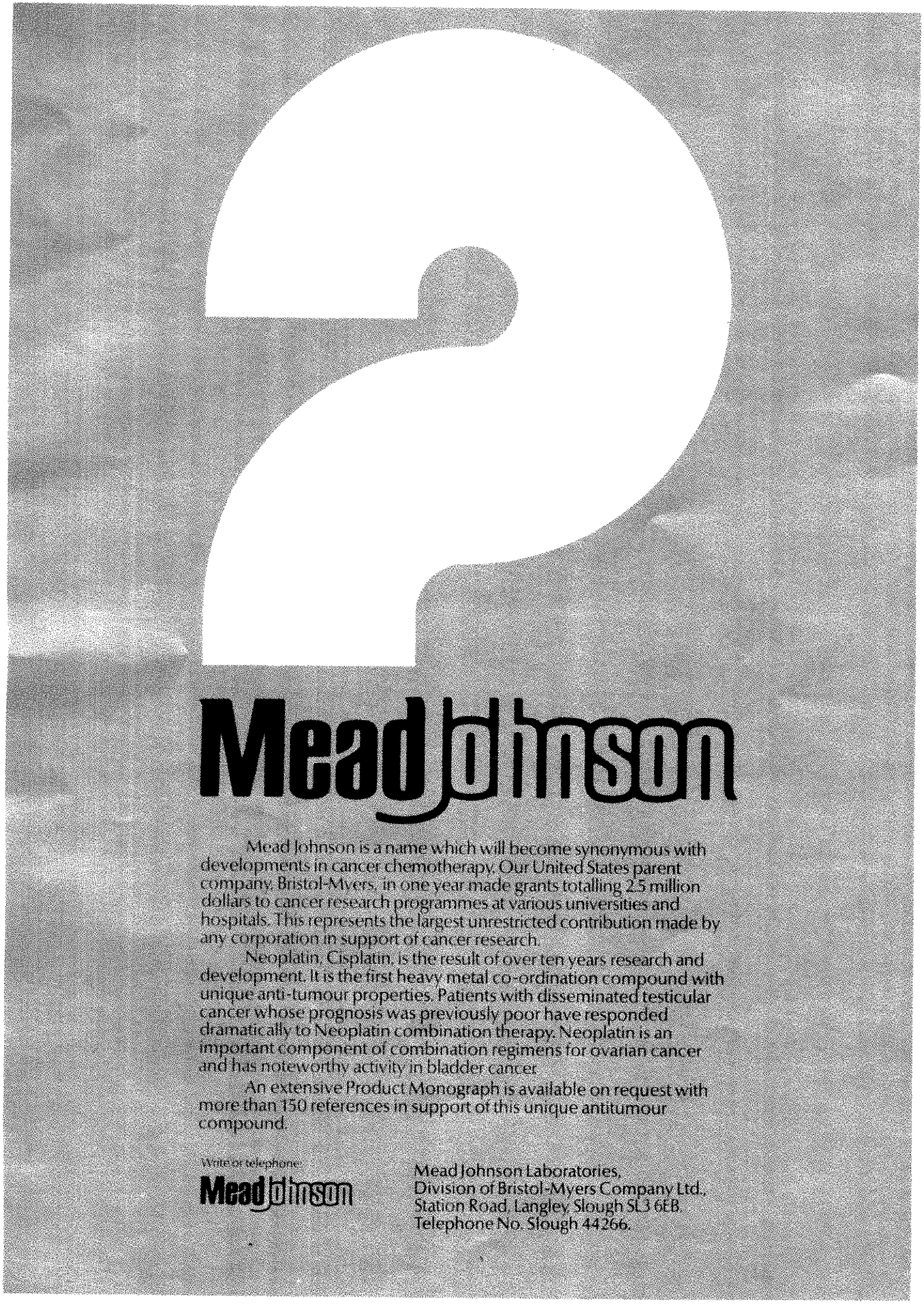

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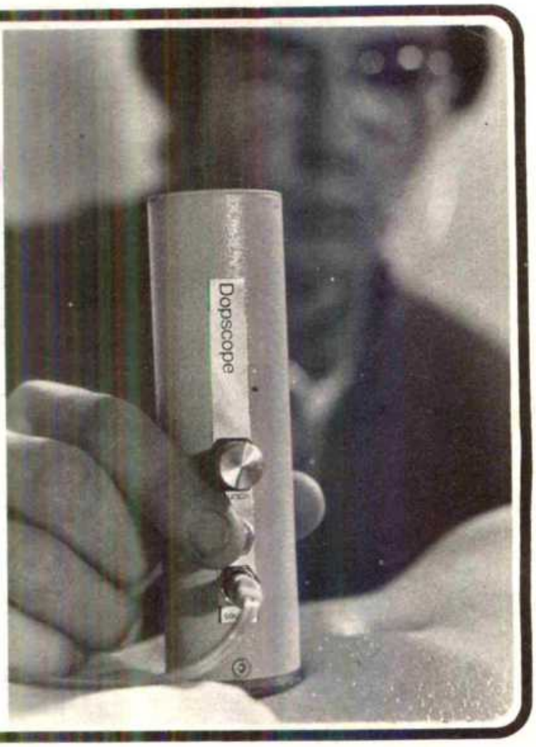

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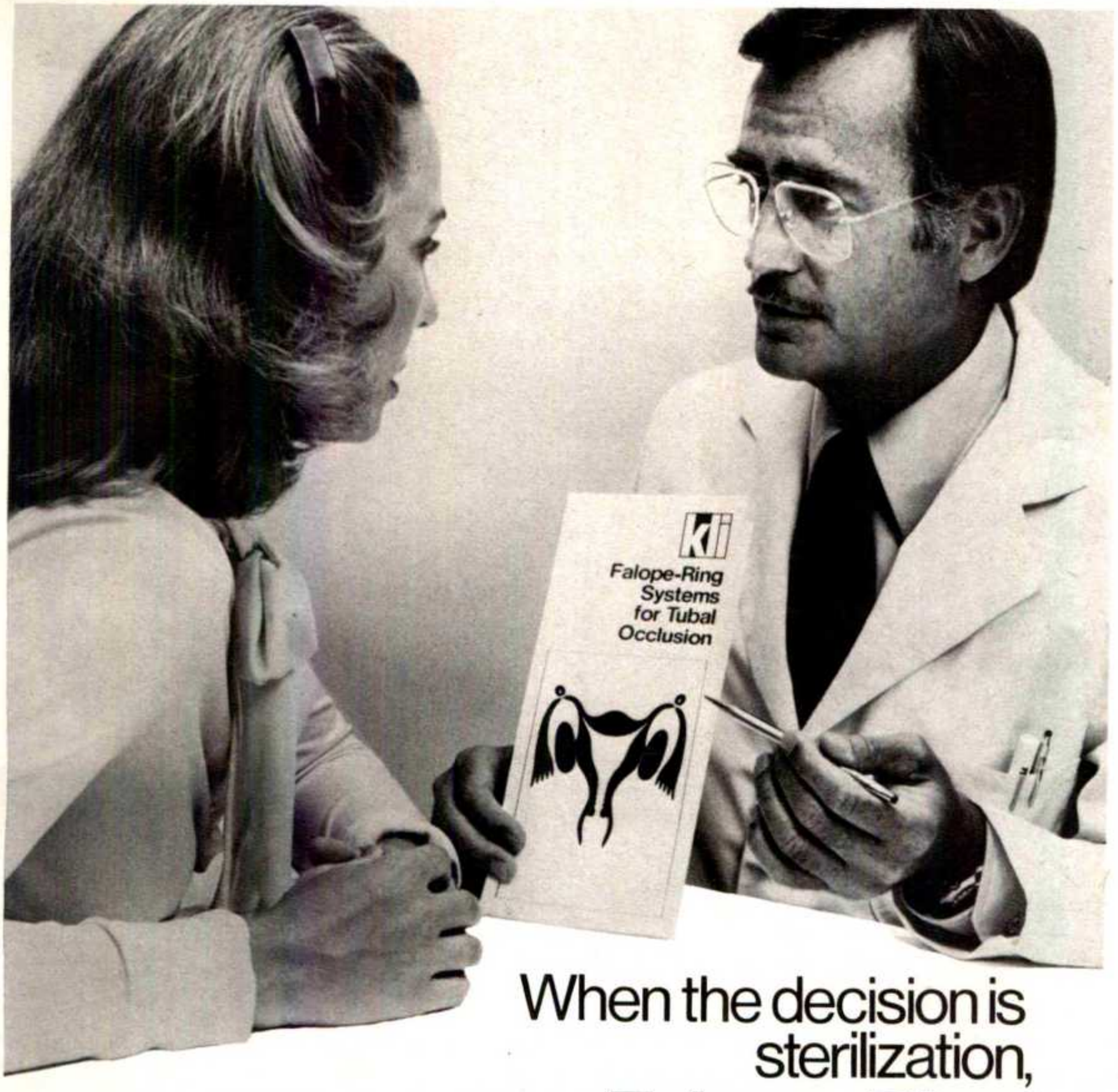

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References 1. *British Journal of Obstetrics & Gynaecology*, **84,** 241–253,1977. 2. *British Medical Journal*, **2,** 694–697,1975. 3. *British Medical Journal*, **2,** 1179–1181,1977. 4. *Current Medical Research & Opinion*, **5,** 734–738,1978. **Indications** Hyperprolactinaemic infertility. Some infertile women without demonstrable hyperprolactinaemia also respond. **Dosage and Administration** Initially 1.25 to 2.5mg nocte; increasing to 2.5mg bd followed by increments of 2.5mg as necessary at 2–3 day intervals. Take with food. **Precautions** Investigate for pituitary tumour. Institute treatment gradually. Withdraw medication immediately pregnancy is suspected. Regular gynaecological assessment is recommended during long term treatment. **Side-Effects** Nausea, postural hypotension, dizziness, headache, vomiting, constipation. **Presentation** 2.5mg tablets of bromocriptine base. **Product Licence Number** 2.5mg tablets PL/0101/0061. **Basic NHS Cost** 30 x 2.5mg tablets £5.93. Parlodel is a registered Trade Mark. Full prescribing information, including product Data Sheet, is available from SANDOZ PRODUCTS LIMITED Sandoz House, 98 The Centre, Feltham, Middlesex TW13 4EP

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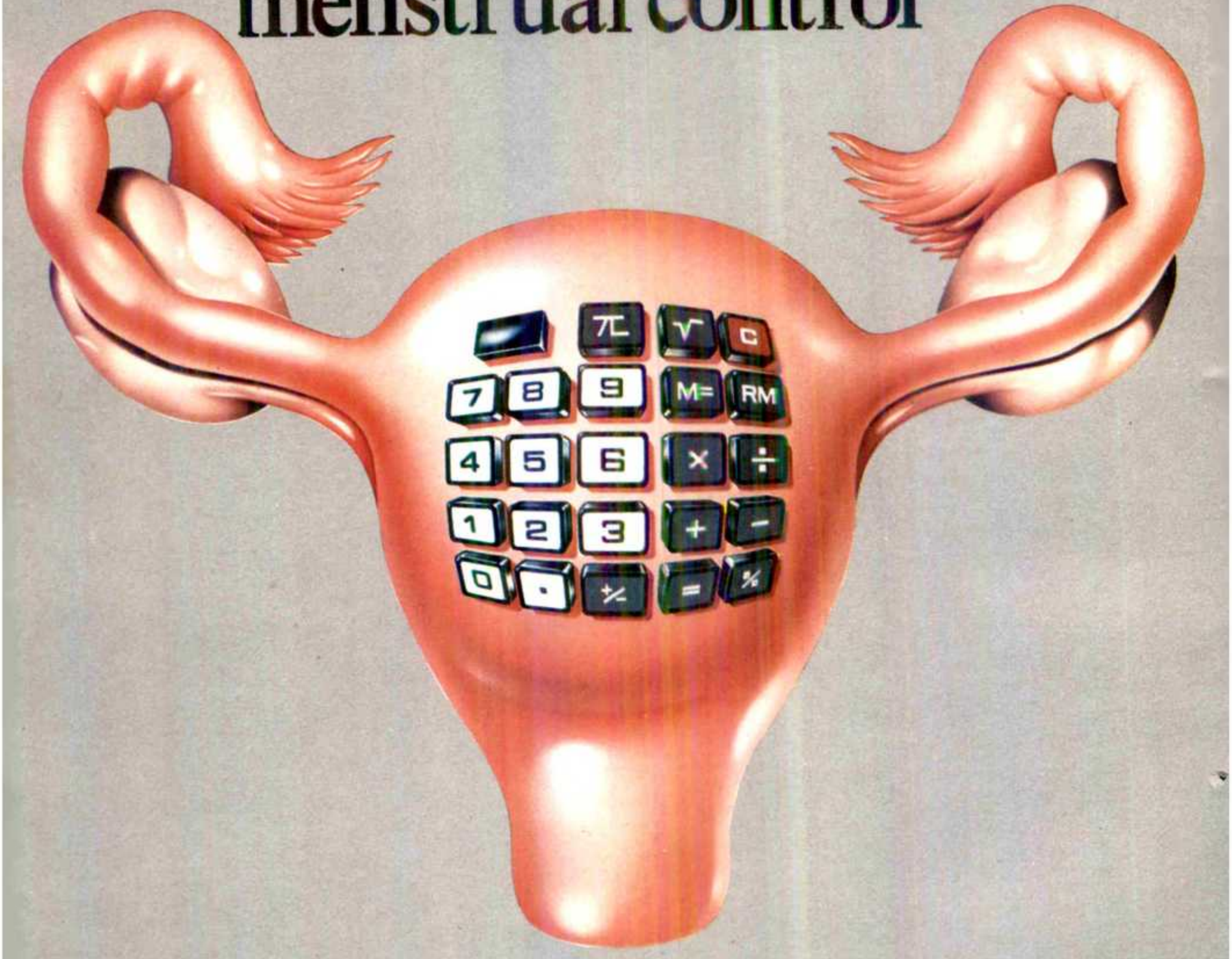

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Vol 86 No. 7 NEW SERIES JULY 1979

THE TREATMENT OF ADVANCED CYSTADENOCARCINOMA OF THE OVARY WITH GESTRONOL AND CONTINUOUS ORAL CYCLOPHOSPHAMIDE

BY

D. GUTHRIE, *Research Fellow*

CRC Oncological Centre, Radiotherapy Department
Newcastle General Hospital, Newcastle upon Tyne

Summary

Fifty-four patients with advanced cystadenocarcinoma of the ovary were treated with gestronol (Depostat), 200 mg/week, by intramuscular injection and continuous oral cyclophosphamide, the dose of the latter being varied to maintain the patient's white cell count at about $1 \cdot 5 \times 10^9$/l. A combined partial and complete remission rate of 76 per cent was obtained. The length of survival depended upon the type of remission and the type of remission was markedly affected by the amount of tumour removed at initial laparotomy.

THE majority of patients with carcinoma of the ovary present with their disease in an advanced state, when only palliative treatment is possible. Alkylating agents have been used for many years to try and induce remission, drugs such as chlorambucil or cyclophosphamide giving combined partial and complete remission rates of 40 to 50 per cent. Usually a standard dose, such as cyclophosphamide 50 mg twice a day, is given but I decided to use the white cell count to determine the dose of cyclophosphamide. In addition gestronol hexanoate (Depostat), 200 mg/week, was given by intramuscular injection, as progestogens alone may induce remission in between 9 and 32 per cent of patients with ovarian cancer (Briggs *et al*, 1967). The results obtained by combining the two drugs are now reported.

PATIENTS AND METHODS

Patients were referred by many consultants in the Northern Regional Health Authority area. All patients had advanced cystadenocarcinoma of the ovary, diagnosed by laparotomy and confirmed by histology. Note was made of the extent of the disease at diagnosis and the amount of tumour not removed.

After ensuring a normal haemoglobin and white cell count, treatment was started seven days after laparotomy by means of daily intravenous injections of 200 mg cyclophosphamide for five days. At the end of this time, treatment was changed to oral cyclophosphamide, 50 mg four times a day, and the patient was usually discharged home. Daily white cell counts were done in hospital and once weekly afterwards. The dose of cyclophosphamide was adjusted to maintain the patient's white cell count at about $1 \cdot 5 \times 10^9$/l. When the count was stable at this level, out-patient visits were cut to once every four weeks, when the haemoglobin and white cell counts were measured and abdominal and pelvic examinations were made, with X-ray and other examinations as appropriate. Gestronol hexanoate (Depostat) 200 mg/week by intramuscular injection was started at the same time as the cyclophosphamide.

If no remission was obtained after eight weeks' treatment, then treatment was stopped. If a remission was obtained, treatment was continued until recurrence of tumour was noted and then stopped. Treatment was stopped in one patient after five years as she was still in complete remission.

Types of remission were defined as follows:

Complete remission. Complete absence of all signs of malignancy on abdominal, vaginal and rectal examination, together with chest X-ray if appropriate.

Partial remission. Marked diminution in the size of the tumour. The common definition of a reduction of 50 per cent or more in the size of the tumour has not been used here, as I am of the strong opinion that such a definition implies a degree of accuracy in assessment which is impossible to achieve.

Symptomatic relief with tumour stasis. Complete relief from all symptoms referrable to the cancer or minimal reduction in tumour size or no appreciable change in tumour size or any combination of these three.

RESULTS

The results of treatment are summarized in Table I and Figure 1.

The dose of cyclophosphamide ranged from

TABLE I

Results of treating 54 patients with a combination of cyclophosphamide and gestronol. Mean length of remission and mean length of survival are calculated from the onset of cytotoxic drug treatment

	Patients		Length of remission (months)		Length of survival (months)		
Remission type	No.	per cent	Mean	Range	Mean	Range	Number still alive
Complete	25	46	15	3–62	18	4–62	7 (range 6–62 months)
Partial	16	30	7	2–22	11	2–26	2 (2 and 5 months)
Symptomatic relief and tumour stasis	5	9	6	3–16	10	4–17	0
No remission	8	15	—		4	1–5	0

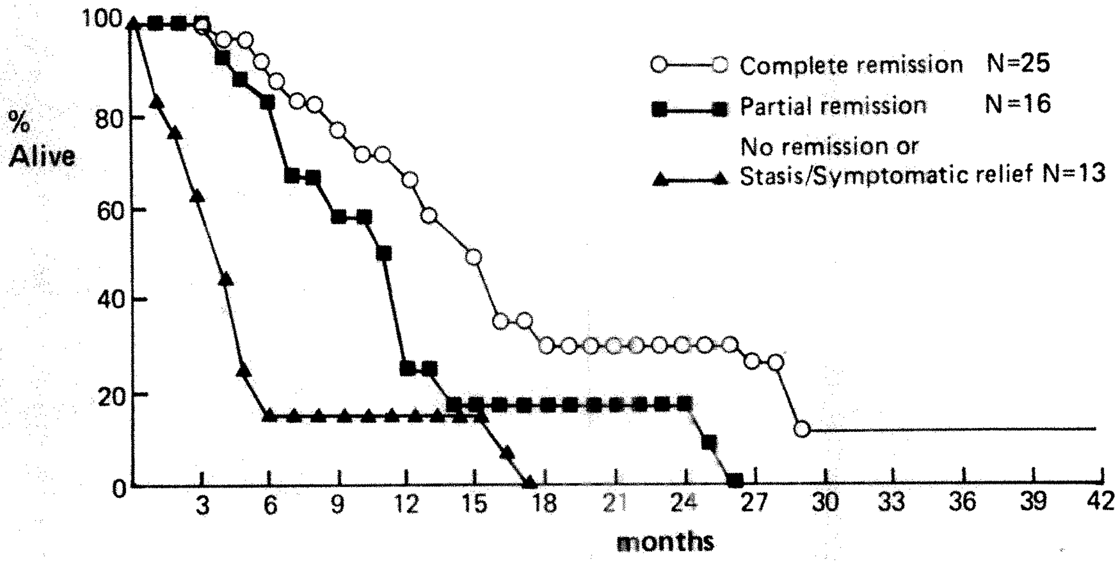

FIG. 1

Time curve relationship for the survival of 54 patients with advanced carcinoma of the ovary treated with cyclophosphamide and gestronol (Depostat). Results are shown according to type of remission.

50 mg to 300 mg/day but the majority of patients had 100 mg or 150 mg/day. It usually took six weeks to reduce the white cell count to the level required and determine the dose of cyclophosphamide to maintain it at that level.

When classified according to the FIGO staging system (F.I.G.O. News, 1971) 12 patients (22 per cent) had Stage IIb ovarian carcinoma, 38 (70 per cent) had Stage III and 4 (7 per cent) Stage IV carcinoma. A higher incidence of complete remission was found in the earlier Stages of disease, the figures being 10 out of 12 patients for Stage IIb, 14 out of 38 patients for Stage III and one out of four patients for Stage IV.

Table II gives the remission rate according to the surgeon's assessment of the amount of tumour removed. When most of the tumour was removed a 77 per cent complete remission rate was achieved as compared with a 25 per cent complete remission rate in that group of patients from whom most of the tumour was not removed.

Fifty patients had a serous cystadenocarcinoma and four had a pseudomucinous cystadenocarcinoma. Of the latter, two had complete remissions and one had a partial remission; one is still alive at 15 months, and the others died at 5, 17 and 26 months after starting any treatment. The degree of malignancy as assessed by histological grading was not analysed.

Nearly all patients had ascites but there was only one patient in whom ascites persisted until her death, three months after the start of treatment. Ascites rarely recurred even when the patient ceased to be in remission, there being only four patients with recurrent ascites at that time.

TABLE II

The effect of the amount of tumour removed surgically on the results of treating 54 patients with a combination of cyclophosphamide and gestronol

	Most tumour removed		Most tumour not removed	
Remission type	No.	per cent	No.	per cent
Complete	17	77	8	25
Partial	2	9	14	44
Symptomatic relief and tumour stasis	0	0	5	16
No remission	3	14	5	16
Total	22	41	32	59

Side effects and problems

Side effects were few and mild. Virtually all patients were able to continue with their normal occupation whilst on treatment.

Only one patient developed a bladder reaction and relief was easily obtained by reducing the dose of cyclophosphamide from 250 mg to 100 mg a day and increasing the fluid intake.

Ten per cent of patients reported some degree of nausea during the first four weeks of oral cyclophosphamide. This always settled spontaneously or could be controlled by prescribing 50 mg of cyclizine to be taken 45 minutes before each dose of cyclophosphamide.

About 60 per cent of patients experienced some degree of alopecia.

Occasionally the white cell count fell below $1\cdot0 \times 10^9$/l but no patient had any ill effects from the leucopenia or the associated platelet deficit.

DISCUSSION

The combined partial and complete remission rate of 76 per cent is certainly better than that previously reported for either cyclophosphamide or chlorambucil alone. Others have tried to improve remission rate by using combinations of drugs. Young *et al* (1976) reporting on the treatment of patients with Stage III and IV ovarian cancers found that melphalan gave a 19 per cent complete remission rate and 42 per cent partial remission rate, in contrast to a combination of 5-fluorouracil, methotrexate, cyclophosphamide and hexamethylmelamine which gave a 33 per cent complete remission rate and 46 per cent partial remission rate. This combined partial and complete remission rate of 79 per cent is marginally higher than that obtained in my series, but their median duration of response was only 8·5 months.

Other workers have tried high doses of cyclophosphamide given intermittently. Geisler *et al* (1976) report on 26 patients with advanced ovarian cancer treated with cyclophosphamide, 50 mg/kg, given intravenously every four weeks for a maximum of 18 doses. They achieved a combined partial and complete remission rate of 88·5 per cent; however, there was no difference in survival after 12 months when compared with other forms of chemotherapy. Their high remission rate was obtained at the expense of nausea and vomiting for 24 to 36 hours after each dose of treatment and also a 19 per cent incidence of haemorrhagic cystitis. That only one of my patients had a bladder reaction must be regarded as fortunate.

The fact that remission type is closely related to the amount of tumour removed at operation is to be expected and has been reported previously. Young *et al* (1976) noted that patients with minimal residual disease had a 45 per cent complete remission rate whereas those with residual tumour more than 2 cm in diameter had only a 23 per cent complete remission rate. The surgeon should thus endeavour to remove as much of the tumour as possible.

The drug treatment I have detailed had very few side effects and gave remission and survival rates which were as good as any yet reported.

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The author thanks the many consultants in the Newcastle upon Tyne area who referred patients for this work and, in particular, Mr Stanley Way, for his great help and encouragement together with the facilities of his department where most of this work was done. The nine patients who are still alive are now under the care of Mr W. M. Ross, and I am grateful for his help and encouragement. Financial assistance was provided by the North of England Council of the British Empire Cancer Campaign for Research.

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HORMONAL PROFILES IN LACTATING AND NON-LACTATING WOMEN IMMEDIATELY AFTER DELIVERY AND THEIR RELATIONSHIP TO BREAST ENGORGEMENT

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Summary

Prolactin, human placental lactogen (HPL), oestrone, oestradiol and progesterone levels in plasma were measured before and during the first seven days after delivery in women who did not breast feed. The results confirmed the rapid clearance of placental steroids from the circulation after delivery. Plasma prolactin levels remained elevated during the early puerperium and the range of values were the same in non breast-feeding women and a group of breast feeding women. Of the 25 women studied, six developed breast engorgement. No difference in hormonal profiles were found leading to the conclusion that there is no endocrine basis for breast engorgement in non-breast feeding women.

DURING pregnancy, the glandular component of the breast proliferates under the action of oestrogens and progesterone, mainly of placental origin. Blood levels of both prolactin and human placental lactogen (HPL) rise progressively throughout pregnancy but their respective roles in mammary development remain obscure (McNeilly, 1977). It is clear, however, that prolactin is the principal hormone involved in milk secretion during lactation (Tyson and Friesen, 1973).

Following delivery, the onset of milk secretion coincides with the clearance of placental steroids from the circulation (Kulski *et al*, 1977), thus allowing the high levels of pituitary prolactin to act on the steroid-primed breast tissue and initiate lactogenesis. Milk secretion begins within 48 to 72 hours of delivery and, in the absence of suckling, ceases within a few days. This spontaneous milk secretion may give rise to breast engorgement.

The degree of breast engorgement which occurs in puerperal mothers who do not breast feed is very variable. Some have marked discomfort and overdistension, while in others the changes are minimal. It has been shown that there is a good correlation between clinical estimation of the degree of breast engorgement and the volume of milk obtained from the breast (Newton and Newton, 1951). The object of our study was to determine whether there was any endocrine basis for the differences in degrees of breast engorgement observed in a group of non-lactating puerperal women.

TABLE I

Clinical assessment of breast engorgement

Score	Milk production	Breast congestion	Breast discomfort
0	No milk leakage	No change	No subjective change
1	Few drops only	Slight hardness	Mild discomfort
2	Moderate leakage	Moderate hardness and redness	Moderate discomfort
3	Marked leakage*	Very hard reddened breasts	Marked discomfort, requiring analgesics

* Requiring frequent changes of breast pad.

PATIENTS AND METHODS

The 25 women who volunteered for the study were all enrolled during the last month of their pregnancies. All had previously decided not to breast feed and none had attempted breast feeding in a previous pregnancy. They all had uncomplicated pregnancies and received no medication other than routine analgesics or antibiotics at any stage during the study. All delivered vaginally, with the exception of two women who had Caesarean sections under epidural anaesthesia.

It is the hospital policy to use no agents to suppress lactation and management is conservative. The women were instructed to avoid handling their breasts and to wear a firm supporting brassière. If uncomfortable symptoms of engorgement developed a firm binder was applied and analgesics offered if necessary.

The degree of breast engorgement was assessed daily during the first week after delivery by the patient herself and by a single observer, using a simple numerical rating system similar to that described in previous studies (Cooke *et al*, 1976; Rolland and Schellekens, 1973). Details of the system are given in Table I. No attempt was made to evaluate milk production by expressing the breast as it was felt that this might interfere with the study. Note was made of the degree of spontaneous outflow. The patient rated the degree of discomfort herself by comparing it with the pre-delivery state and an assessment was made of the degree of congestion by gentle palpation and observation of distension and overlying skin changes. The final assessment of degree of engorgement in each individual was obtained by adding together the three highest daily scores obtained during the six days of the study. For comparison, blood samples were taken at least two hours after a suckling episode from 17 women who were breast feeding their babies.

Ten ml venous blood samples were taken at the time of enrolment to the study, within an hour of completion of the third stage of labour and daily during the first six days of the puerperium. In some subjects, blood samples were taken twice daily during the first 72 hours of the puerperium. The blood was immediately centrifuged and stored at −20°C until the assays were performed.

Hormone assays

Plasma prolactin was measured by a specific double antibody radioimmunoassay using reagents supplied by Professor H. G. Friesen, Winnipeg, Canada (Hwang *et al*, 1975; McNeilly and Hagen, 1974). The inter- and intra-assay precision was 13 per cent and 6 per cent

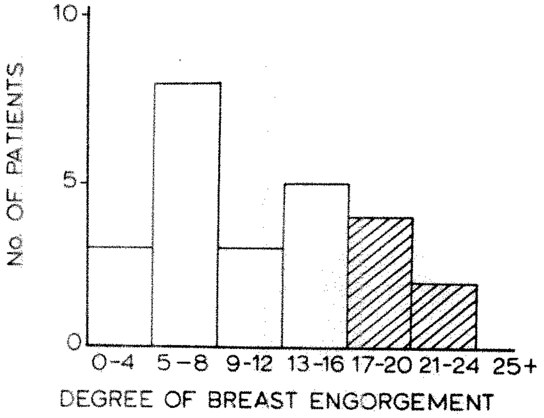

FIG. 1

Distribution of patients in relation to the degree of breast engorgement. Patients showing scores greater than 17 (hatched columns) showed severe clinical signs of breast engorgement.

respectively. Plasma human placental lactogen (HPL) was measured using the Phabedas kit (Radiochemical Centre, Amersham). Progesterone, oestrone and oestradiol in plasma were measured by previously described radioimmunoassays (Baird *et al*, 1974; Scaramuzzi *et al*, 1976; Van Look *et al*, 1977).

RESULTS

The mean age of women entering the study was 26 years (range 19 to 34) and 17 of them were parous. The degree of breast engorgement is shown in Figure 1. The six women with the greatest degree of engorgement (score of more than 17) will be considered separately later.

The mean and range of plasma levels of progesterone, oestradiol, oestrone and HPL in the six women with severe breast engorgement are shown in Figure 2. At no time did the levels for any of these hormones fall outside the range of levels found in the non-lactating group as a whole, even when the breast-engorged subjects

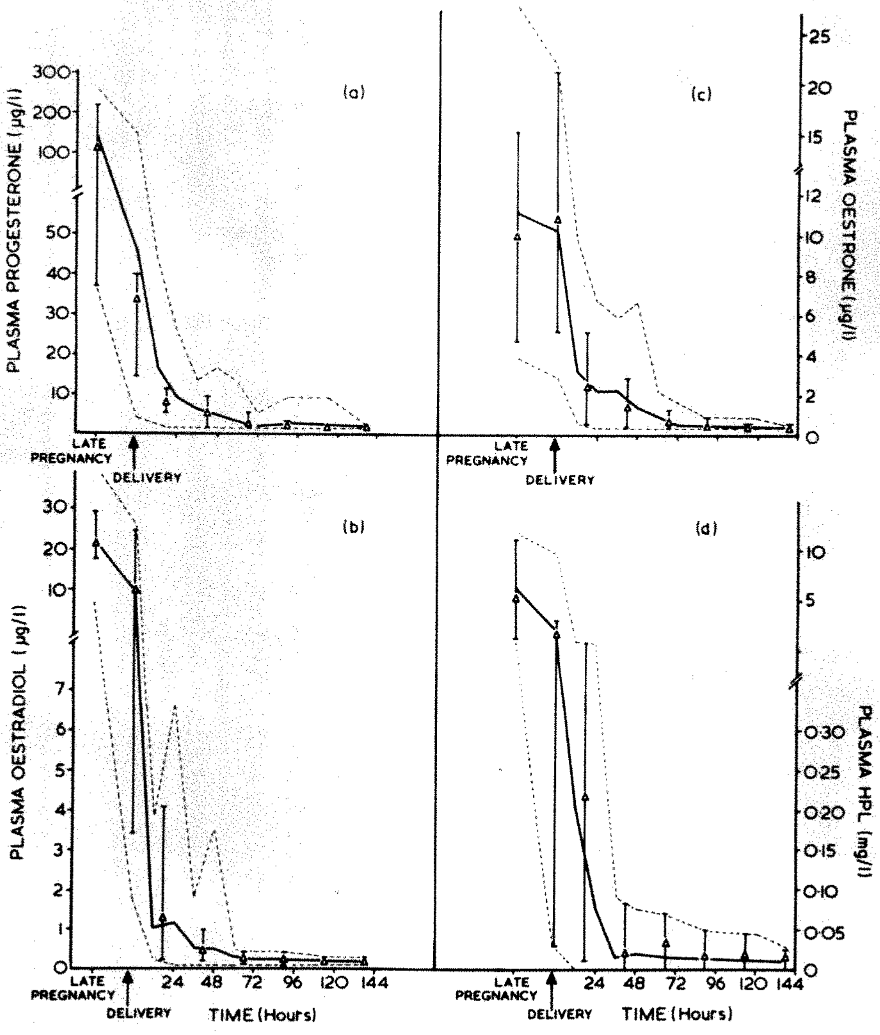

FIG. 2

Plasma levels of (a) progesterone, (b) oestradiol, (c) oestrone and (d) HPL immediately before and for six days after delivery in non breast-feeding women (n = 25). The mean value (solid line) and range (dotted lines) are shown for each hormone. The mean (△) and range of hormone levels for the six patients showing severe breast engorgement are also shown.

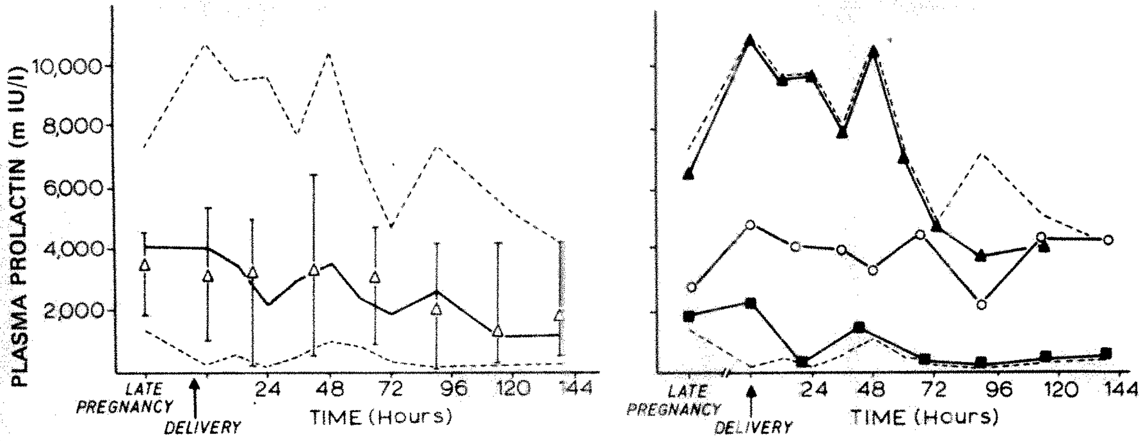

FIG 3.

Plasma levels of prolactin immediately before and for six days after delivery in non breast-feeding women (mean = solid line; range = dotted lines. (a) The mean (△) and range of plasma prolactin levels for all six patients showing severe engorgement. (b) Serial prolactin levels in each of three patients with breast engorgement—scores of 15 (▲), 17 (○) and 19 (■).

were excluded. No difference was seen in the levels of these hormones in late pregnancy (Fig. 2).

Plasma prolactin levels in those subjects with breast engorgement are shown in Figure 3 (a). The mean and range of values lie within the range of plasma levels of prolactin in the non-breast feeding group as a whole. The individual sequential values for plasma prolactin in three of the breast-engorged women are shown in Figure 3 (b). It can be seen that the level of prolactin was not related to the degree of breast engorgement, the highest basal levels of prolactin being associated with less severe breast engorgement (score = 15) than the lowest overall prolactin levels (score = 19). This is further emphasized when comparison is made of the individual degree of breast engorgement as estimated clinically and the mean prolactin level obtained during the first six days after delivery. No significant correlation was found (Fig. 4).

The mean and range of prolactin levels obtained during the study of the 25 non-lactating mothers was comparable to that of the basal levels of prolactin in a group of 17 breast feeding mothers (Fig. 5). Blood samples were taken at least two hours after a period of breast feeding in the latter group.

DISCUSSION

The endocrine events of the early puerperium in relation to the onset of milk production are of considerable interest, not only in relation to chemical suppression of unwanted lactation and in the understanding of the potential adverse effects of contraceptive steroids on milk production, but also to those concerned with developing methods of enhancing poor lactation in mothers attempting to breast feed. There are no other studies in the literature in which these changes are considered in a group of non-lactating women.

Our object was to study the endocrine changes and degree of breast engorgement in women undergoing no form of suckling stimulus. We felt that our results might throw some light on the marked differences in lactational performance seen in puerperal women who breast feed their infants. While it is known that frequent suckling is important for the success of lactation (Egli *et al*, 1961), the fact that breast engorgement occurs in some women who do not suckle suggests that the ability to produce milk is not related simply to suckling. It has also been shown (Illingworth and Stone, 1952) that lactating women who experience breast engorgement during the initial stages of lactation subsequently breast feed more successfully than those who have no engorgement.

The results of our study clearly show that there is no obvious endocrine basis for the differences in degree of breast engorgement experienced by non-lactating puerperal women.

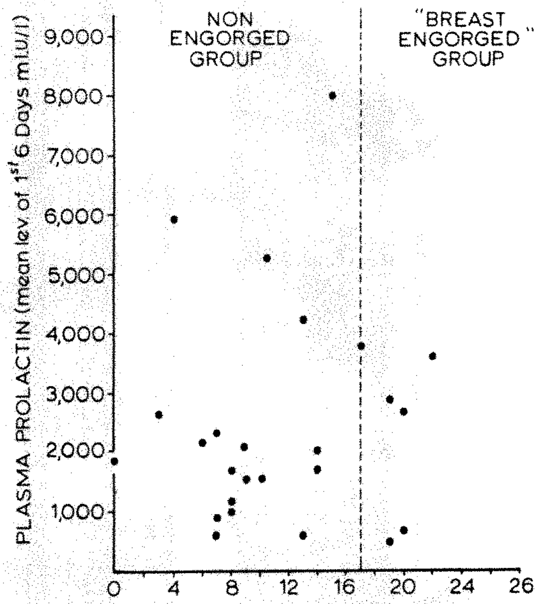

FIG. 4

Correlation between plasma levels of prolactin (mean plasma level over the first six days after delivery) and the degree of breast engorgement.

They confirm the results of previous studies showing that levels of oestrogen and progesterone fall sharply following delivery, while levels of prolactin fall more gradually during this period (Reyes *et al*, 1972; Bonnar *et al*, 1975). Since lactation can be completely inhibited with bromocriptine which suppresses prolactin levels into the non-pregnancy range (Cooke *et al*, 1976), it is clear that prolactin is essential for lactation. It was therefore considered possible that the degree of breast engorgement in non breast-feeding women might relate to the levels of prolactin in the early puerperium.

A marked individual variation in prolactin levels was seen during the period of the study, levels remaining elevated in some women throughout the first six days of the puerperium, while in others levels fell rapidly to the non-pregnant range within three days. It is interesting that, at this early stage of the puerperium, ranges of prolactin levels in non-lactating women were comparable to basal levels seen in a group of mothers who were breast feeding. Our results clearly suggest that there is no direct relationship between the degree of breast engorgement, presumably related to the ability of the breast to secrete milk, and the actual level of circulating prolactin.

The onset of lactogenesis and milk secretion in human lactation appears to closely parallel the disappearance of steroid hormones from the circulation after delivery (Kulski *et al*, 1977).

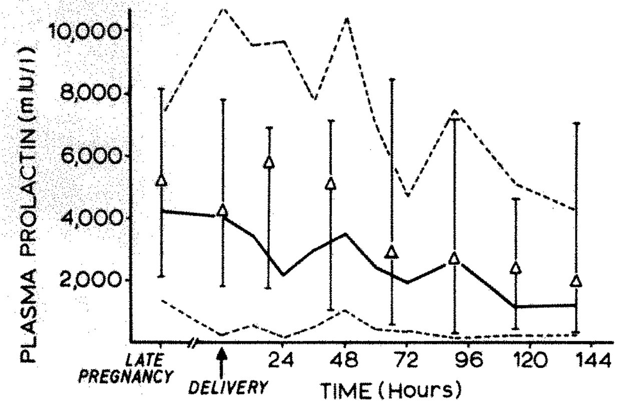

FIG. 5

Plasma levels of prolactin before and for the first six days after delivery in non breast-feeding women (mean = solid line, range = dotted line, n = 25) and in a group of breast-feeding women (mean (△) and range, n = 17).

It is uncertain which of the placental steroids acts as the inhibitor, or how this inhibition is brought about but recent evidence suggests that the active steroid may be progesterone (Hartmann *et al*, 1973; Kulski *et al*, 1977) as in animals. Nevertheless lactation may be inhibited by treatment with oestrogens (Daniel *et al*, 1967).

Overall increase in breast volume during pregnancy appears to determine subsequent milk output (Hytten, 1954). This suggests that local factors in the breast are likely to be relevant in determining its potential for milk production. In our study, the six women with the highest scores, and thus with the most marked degree of breast engorgement, were selected for comparison with the group as a whole. Only 4 out of the 25 women, all in the 'engorged' category, actually required analgesics to relieve breast discomfort and the majority were aware of mild discomfort only. One clinical study of postpartum breast engorgement concluded that placebo was effective in relieving symptoms of engorgement in 90 per cent of subjects and hence the universal use of agents to suppress lactation was unjustified (MacDonald and O'Driscoll, 1965). Our findings seem to support the view that such agents are of benefit only to a minority of women and thus suppressive therapy should be selective.

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CUT-OFF LEVELS FOR MATERNAL PLASMA ALPHA-FETOPROTEIN IN THE DIAGNOSIS OF NEURAL TUBE DEFECTS: VALIDATION OF THE USE OF MULTIPLES OF THE NORMAL MEDIAN

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Summary

A retrospective study was made of measurement of maternal plasma alpha-fetoprotein (AFP) by a standard radioimmunoassay technique, as a method of screening for neural tube defects (NTDs) between 15 and 20 weeks gestation. There was a good fit of a log-normal distribution to the data at each week and multiples of the normal median were equivalent to constant centiles over weeks 15 to 20 and possibly at later weeks also. There were 700 plasma samples from women with normal pregnancies and 60 from women with pregnancies complicated by fetal NTDs (30 with anencephaly and 30 with spina bifida). At 15 to 20 weeks of pregnancy, 90 per cent of women with fetuses affected by anencephaly, 70 per cent of those with fetuses affected by open spina bifida and 3 per cent of those with normal pregnancies had plasma AFP levels at or above 2·4 times the normal median for each gestational week. It was estimated that 2·1, 2·4 and 3·1 times the normal median maternal plasma AFP levels were equivalent to the 95th, 97th and 99th centiles respectively. The interassay coefficients of variation estimated on control sera throughout the entire study were 4 to 6 per cent.

THE United Kingdom (UK) Collaborative Study (1977) described the measurement of maternal serum AFP levels, by a variety of radioimmunoassay techniques, as a screening method for the detection of fetal neural tube defects (NTDs) between 10 and 24 weeks gestation. Data were collected from 19 centres, on 18 684 normal pregnancies and on 301 affected pregnancies. At 16 to 18 weeks gestation, 88 per cent of women with fetuses affected by anencephaly, 79 per cent of those with fetuses affected by open spina bifida and 3 per cent of those with normal pregnancies had AFP levels at or above 2·5 times the median (equivalent to approximately the 97th centile) for normal pregnancies. The results were presented in terms of multiples of each participating centre's normal median and the data were analysed within separate reporting periods to allow for changes in each centre's normal range.

A report from the West of Scotland (Ferguson-Smith *et al*, 1978) described the screening of 11 585 pregnant women, between 16 and 20 completed weeks gestation, by measurement of serum AFP levels using a radioimmunoassay. In the second phase of the study it was stated that the intervention point was an estimated 97th centile which corresponded to 2·8 times the normal median; only 1·4 per cent of unaffected pregnancies had AFP levels above this cut-off point.

Our study is concerned with screening for

NTDs by measurement of maternal plasma AFP using a single radioimmunoassay technique. The results correspond in some important respects to those of the UK Collaborative Study (1977) and we present arguments in favour of using multiples of the normal median for the interpretation of results between 15 and 20 weeks gestation.

METHODS

Terminology

We define normal (or unaffected) pregnancy as a singleton pregnancy not complicated by a fetal NTD. Pregnancies in which the fetus had an NTD are referred to as affected pregnancies or NTD pregnancies. Gestational age was measured in completed weeks from the first day of the last menstrual period. AFP 'level' and AFP 'value' are used as synonyms for AFP concentration.

Samples

Plasma samples collected in heparin were obtained by Dr D. H. J. Brock, University Department of Human Genetics, Edinburgh, from pregnancies where the gestational age was known. The condition of the infants after birth was also known. The samples were collected over a period of about three years and stored at −20°C.

Blood samples were not taken serially from any group of patients. For normal pregnancies there were ten plasma samples at each week between 10 and 14 weeks gestation; 100 samples at each week between 15 and 20 weeks and ten samples at 22, 24, 26, 28 and 30 weeks. For NTD pregnancies there were ten plasma samples at each week between 15 and 20 weeks gestation.

Assay methods

Highly purified human AFP prepared as described by Nishi (1970) was used to prepare a specific rabbit anti-human AFP serum which was used in the assay at a final dilution of 1 in 30 000. ^{125}I-AFP was prepared according to a standard method (Greenwood *et al*, 1963). A series of accurately calibrated standards was made from human AFP and normal human serum. Polyethylene glycol 6000 was obtained from British Drug Houses.

Samples of plasma or standards measuring 100 μl were pipetted into polystyrene tubes; 100 μl of ^{125}I-AFP (20 μCi/μg) were added to a final concentration of 3·3 ng/ml, followed by 100 μl of anti-AFP serum. After vortex mixing the tubes were allowed to stand overnight (18 to 24 hours) at room temperature (15 to 30°C); 1 ml of aqueous polyethylene glycol was added to all tubes, the contents were mixed and the tubes centrifuged for 10 minutes at 1500 *g*. The supernatants were removed by decantation and the precipitates counted in a gamma-counter. The concentration of AFP in the samples was calculated with reference to a standard curve effective over the range 0 to 400 ng AFP/ml.

The standards used in the assay were initially calibrated against highly purified AFP dissolved in normal human serum to give a scale in terms of absolute units. Subsequently, dilutions of the British Standard (72/227) were measured in the assay to give a conversion factor. The results are summarised in Table I. It should be noted that almost perfect parallelism with the assay standards occurs when the human serum AFP reference standard is diluted and simultaneously measured.

The entire range of maternal plasma samples was assayed with reagents produced and tested

TABLE I

Assay of British Standard (72/227)

Dilution	Units/ml	AFP concentration (ng/ml)			
		Assay 1	Assay 2	Assay 3	Mean
1 in 250	394	379	378	368	375
1 in 500	197	193	170	183	182
1 in 1000	98·5	92	85	101	93
1 in 2000	49·25	47	46	47	47

The mean conversion factor calculated for the British Standard is given as 1 ng AFP = 1·06 British Units.

TABLE II

Reproducibility data as measured on control sera

	Control sera			
	A	B	C	D
Number of assays	36	36	36	36
Mean value (ng AFP/ml)	27·6	57·6	118	297
Coefficient of variation (per cent)	5·9	3·9	3·9	4·9

according to a quality control schedule. The samples were measured in a wide range of assays in such a way that differences between weeks, or differences between unaffected and affected pregnancies, were not confounded with assay to assay differences. The variation between samples in any one week was in any case very much greater than measurement error so that the latter could be largely ignored.

Control sera designated A, B, C and D were included in all assays. The means and coefficients of variation of the control serum values are given in Table II. In the calculation of these results none of the values were rejected from any of the assays.

RESULTS AND DISCUSSION

Plasma AFP from normal pregnancies

It is clear from the data on normal pregnancies that within any single gestational week the distribution of concentrations of AFP was not symmetrical. True values below zero cannot occur but there were a number of samples with relatively high concentrations. The model that is most likely to apply in this case is the log-normal distribution (which means that the logarithms, to any base, of the values have a normal distribution).

In order to test this assumption, a cumulative frequency diagram of the logarithms (base 10) of the data was plotted on normal probability paper for each of gestational weeks 15 to 20. Zero values could not actually be plotted but account was taken of their existence in positioning all other points. Centiles used for plotting were: $i/(n + 1)$ (where i = position of each result in the ordered data). For further details of probability plots see Gerson (1975).

In the region of AFP values above about 15 ng/ml, the resulting plots were very well fitted by straight lines (for an example see Fig. 1). The only exception in all six plots was the single highest value observed in week 20. This indicates a good fit of almost all the data in this region to a log-normal distribution. Because of the rather small number of values in the upper tail of the distribution, larger studies will be required to fully confirm this conclusion. At least part of the reason for the departure from log-normality below about 15 ng/ml was that the percentage coefficients of measurement variation were quite high in the region of zero (as compared with 4 to 6 per cent elsewhere).

This behaviour at low concentrations in conjunction with the occasional possible outlier at the upper end of the distribution would justify the use of the sample median as a robust estimator of the location of the distribution, rather than the sample mean which would be unduly affected by these extreme values. The same also applies to estimators of a measure of spread, where an intercentile range (eg half the range 16 to 84 per cent) would certainly be preferable to the sample standard deviation as an estimator of the true standard deviation.

The method actually used was thought to combine these virtues of robustness with improved precision of estimation. Straight lines were fitted to the cumulative frequency plots giving least weighting to points in the lower 20 per cent and upper 10 per cent of the distributions. From these the median and standard deviation of each normal distribution of the log-data were estimated and the 95th, 97th and 99th centiles read off the linear smoothing of the graph. In practice the difference between the upper centiles estimated from these plots and the corresponding non-parametric estimates was always small.

The robust estimates of standard deviation were all close to each other and with no apparent trend. A statistical test of the actual spread of these estimates compared with their expected spread if they were all estimates on 99 degrees of freedom gave a value of 8·5 to be compared with the χ^2_5 distribution (whose upper 5 per cent point is 11). Thus the scatter of estimates was well within the limits of sampling error that would be obtained if all the normal distributions had the same standard deviation; the best estimate for this parameter was 0·2. For gestational weeks 22, 24, 26 and 28 the standard deviations of the log-normal distributions were 0·26, 0·21, 0·20 and 0·19 respectively and there was no indication of a systematic difference from the previous weeks (15 to 20) gestation. However, for the late weeks the numbers involved were too small for any firm conclusions. Earlier weeks could not be usefully compared since such a high proportion of measurements were at or below 10 ng/ml.

In terms of the original data, this conclusion

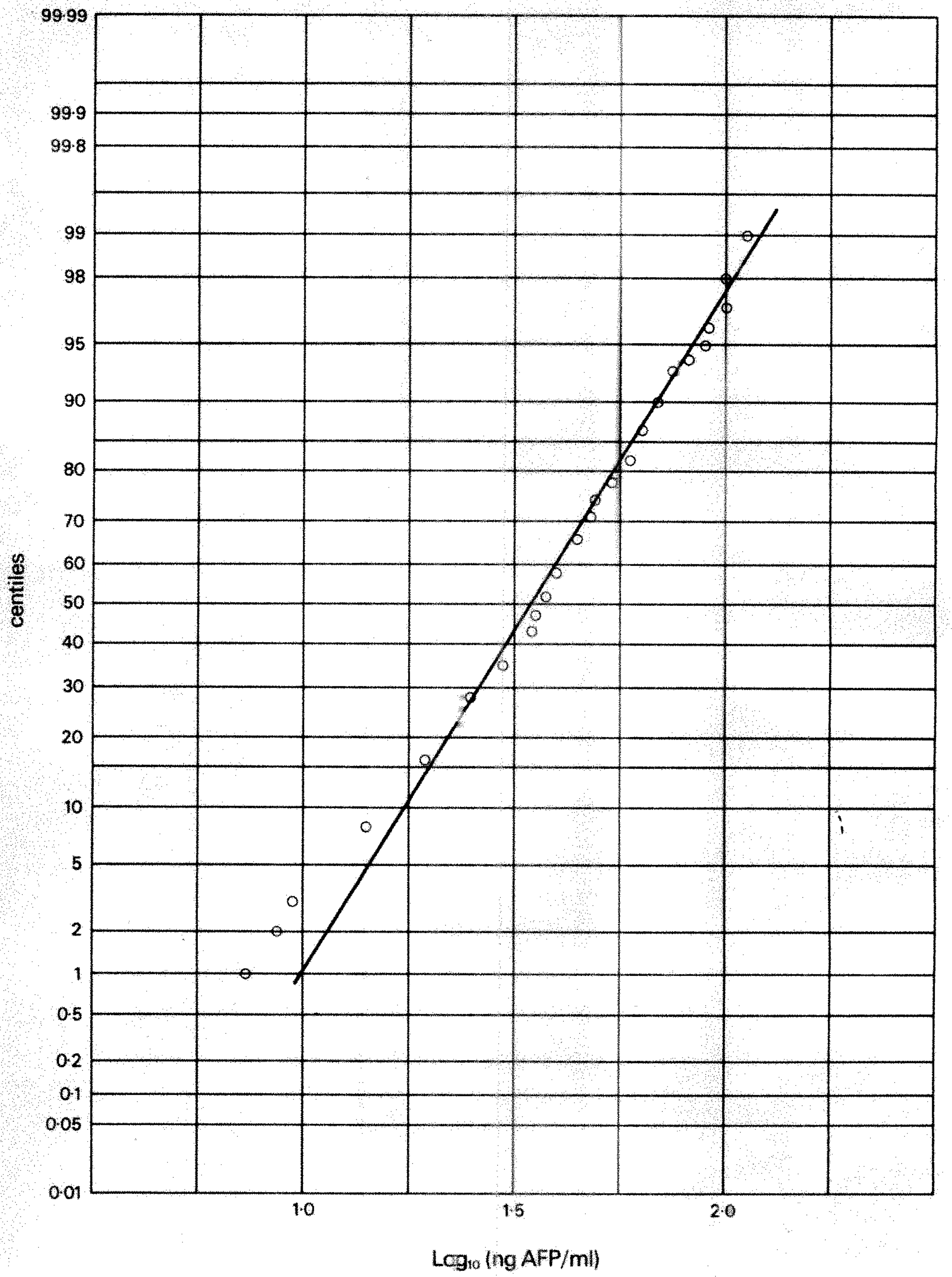

FIG. 1

Cumulative frequency plot, on normal probability paper, of the logarithms of maternal plasma AFP values for 19 weeks gestation

TABLE III

Estimates of the median, 95th, 97th and 99th centiles of the distribution of maternal serum AFP levels from normal pregnancies at different gestational weeks

Week of gestation	Serum AFP (ng/ml)				Centile: Median ratio		
	Median	95th centile	97th centile	99th centile	95th	97th	99th
15	20·4	40·7	45·7	55·0	2·0	2·2	2·7
16	30·9	67·6	75·9	93·3	2·2	2·5	3·0
17	30·2	67·6	75·9	95·5	2·2	2·5	3·2
18	33·9	69·2	75·9	93·3	2·0	2·4	2·8
19	35·5	85·1	95·4	123·3	2·4	2·7	3·4
20	45·7	95·5	104·7	125·9	2·1	2·3	2·8
Overall best estimate of ratio					2·1	2·4	3·1

implies that the coefficients of variation for the population distributions of actual values at any stage from 15 weeks onwards remained constant. This was not an artefact of assay to assay variation since this was relatively small. Table III shows the medians and important centiles of the original data for weeks 15 to 20. For a single centile, the ratios of the centile: median for each gestational week were close to one another, with no apparent trend. These findings support the use of the median and multiples of the median (which are equivalent to constant centiles) for establishing cut-off points for concentrations of AFP in the normal population, at least for gestations of 15 to 20 weeks and possibly by extrapolation to later dates also.

Linear regression analyses were made against gestational age for the medians and upper centiles of the log-data. No evidence of non-linearity was found. Figure 2 shows the lines of best fit for the logs of the medians and 97th centiles for weeks 15 to 20 inclusive and their relation to the values for previous and subsequent periods. As expected from the discovery of a constant standard deviation, the regression lines were virtually parallel. Indeed the closeness of the estimates of b (slope), as shown in Table IV, was remarkable.

TABLE IV

Estimates of regression coefficients

Estimator	a + bx	Standard error of b
Median	1·36+0·057x	0·012
95th centile	1·68+0·060x	0·014
97th centile	1·73+0·060x	0·015
99th centile	1·82+0·061x	0·016

x = gestational age − 15

In terms of the log-data, AFP values appeared to increase linearly with time from 15 to 20 weeks gestation, and possibly considerably beyond this (see Fig. 2). From this data the best estimates of the ratios for the 95th centile: median, 97th centile: median and 99th centile: median were 2·1, 2·4 and 3·1 respectively.

Before 15 weeks gestation, the log-median AFP values deviated from linearity. However, these medians were estimated from only 10 results and many of the values were measured near the sensitivity limit of the assay. If the linear regression line for the medians was extrapolated back to zero weeks of pregnancy, the intercept on the y axis equalled 3 ng AFP/ml.

Wald (1976) previously pointed out that, given a log-normal distribution of maternal serum AFP values, multiples of the normal median would be equivalent to constant centiles providing the standard deviation was similar from one gestational week to another. However, the data available at that time were incomplete (and subject to change with improvements in assay performance).

The UK Collaborative Study (1977) suggested that the multiple of the median corresponding to a given centile decreased with age of gestation

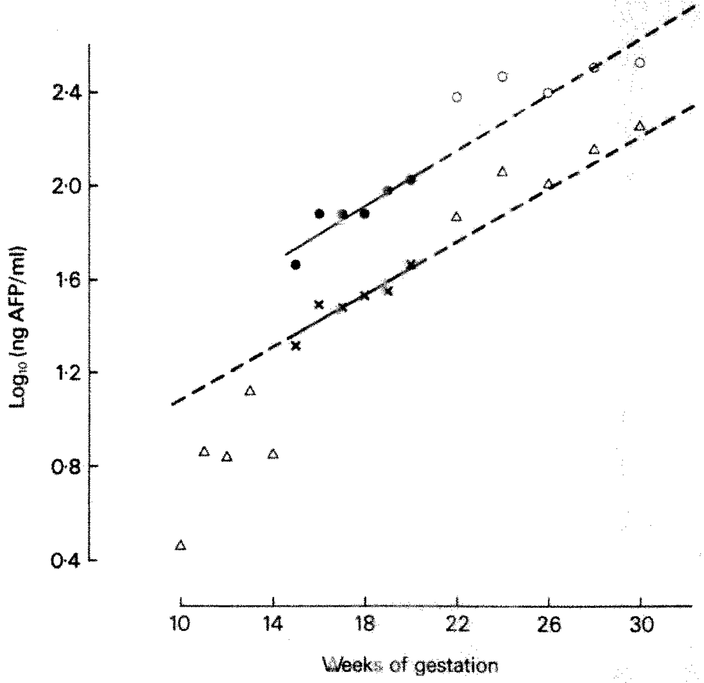

FIG. 2

Linear regression lines fitted to estimates of the medians and 97th centiles of the log-normal distributions of AFP values in maternal plasma. ———— —— —— — = regression lines estimated from 15 to 20 week data; X = median estimated from 100 values; △ = median estimated from 10 values; ● = 97th centile estimated by extrapolation from 100 values; ○ = 97th centile estimated by extrapolation from 10 values (imprecise estimate included to show trend).

over 10 to 21 weeks whereas the data from our investigation suggests that it remains constant at least over 15 to 20 weeks gestation. If, however, the 16 to 21 week period from the UK Collaborative Study (1977) is considered then the two sets of results are in much closer agreement. For example in the UK Collaborative Study (1977) the ratio of the 90th centile: median was 1·87 for 16 to 18 weeks and 1·86 for 19 to 21 weeks gestation. This ratio in our study was 1·81.

The data from our study are too few to allow a firm conclusion that given multiples of the median define constant centiles over the stated gestational weeks. Further analysis on more extensive data will be required to clarify whether the standard deviation of log AFP can, for practical purposes, be regarded as constant from week to week. Additionally, it should be emphasised that only in the absence of significant fluctuations in errors associated with the AFP assay or measurements of gestational age could a given multiple of the median (previously calculated to correspond to a particular centile) be applied with consistent results throughout a screening programme.

In the second phase of the West of Scotland Study (Ferguson-Smith *et al*, 1978) in which 11 585 pregnancies were screened, a constant multiple of 2·8 times the median was used as an intervention point over 16 to 20 weeks. From their data it was evident that this multiple of the median approximated to the 98·6th centile as this intervention level gave 1·4 per cent false positives. The false positive rate could be reduced to 1·0 per cent by exclusion of twin pregnancies or those with missed or threatened abortion. Although the figures are not quite comparable in their present form (since actual proportions of multiple pregnancies and threatened abortions in the West Scotland population were not given) it is clear that there is remarkably good agreement with the estimate derived from our study that 2·8 multiples of the median approximate to the 98·7th centile.

As shown above, a comparison of our study, the UK Collaborative Study (1977) and the West of Scotland Study (Ferguson-Smith *et al*, 1978) indicates good agreement over the specific multiples of the median which correspond to particular centiles, within a limited gestational period. This result could be fortuitous; the

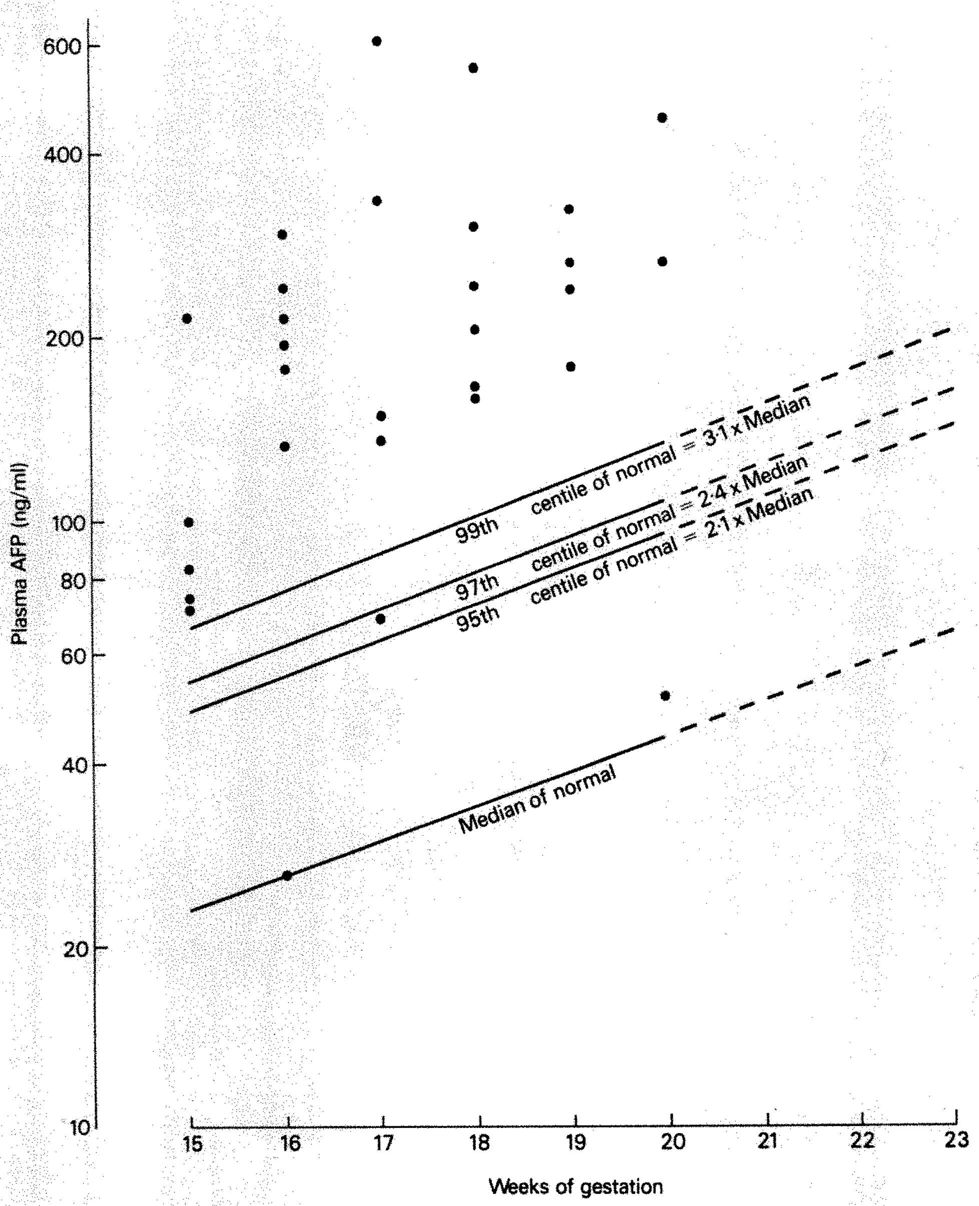

FIG. 3

Maternal plasma AFP values of pregnancies with fetal anencephaly in relation to the median and upper centiles of the values from normal pregnancies.

average errors associated with the AFP assays and the measurements of gestational age may have been similar in all three studies. It would be of value if further studies from other centres could be run in conjunction with a quality control scheme so that the precision and accuracy of the assays done could be compared.

Plasma AFP from pregnancies with NTDs

Figures 3 and 4 indicate the proportion of NTD pregnancies detected at the 95th, 97th and 99th centiles of normal at different weeks of gestation. For anencephaly (30 fetuses), the detection rate showed no particular trend over 15 to 20 weeks. For open spina bifida (24 fetuses), the detection rate apparently increased until 17 weeks gestation. However, the number of affected pregnancies at each gestational week were far too small to allow any firm conclusions to be drawn.

Table V summarises the proportion of af-

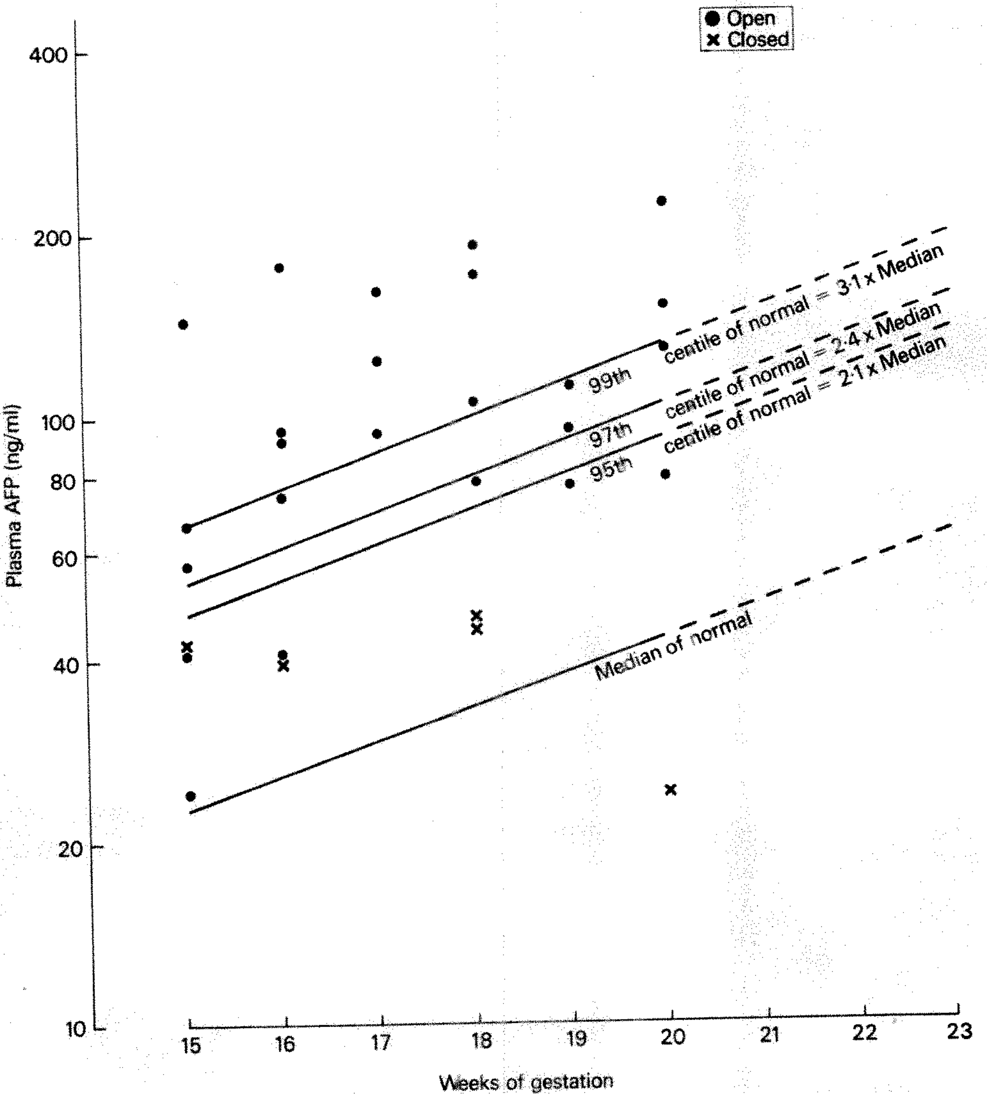

FIG. 4

Maternal plasma AFP values of pregnancies with fetal spina bifida in relation to the median and upper centiles of the values from normal pregnancies.

TABLE V

Observed percentage of pregnancies with maternal plasma AFP levels at 15 to 20 weeks gestation equal to or greater than specified cut-off levels

Pregnancy	Cut-off level (multiple of normal median) 2·1	2·4	3·1
Singleton NTD pregnancies:			
Anencephaly	93	90	90
Spina bifida	83	79	54
Normal pregnancies	4	3	1

fected and normal pregnancies at 15 to 20 weeks gestation, which had AFP levels equal to or greater than three different multiples of the median. Similar detection efficiencies for NTDs have been obtained to those published in the UK Collaborative Study (1977).

It has been advocated (UK Collaborative Study, 1977) that in clinical practice it is more convenient to use multiples of the median AFP value as intervention points (they may be determined accurately with relatively few results) rather than attempt to estimate the upper centiles of the distribution. The study reported here has helped to justify this approach.

ACKOWLEDGEMENT

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THE RELATION BETWEEN MATERNAL SERUM ALPHA-FETOPROTEIN LEVELS AND FETOMATERNAL HAEMORRHAGE

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Summary

Spontaneous fetomaternal haemorrhage at 14 to 20 weeks gestation resulted in raised serum alpha-fetoprotein (AFP) levels in 13 of 150 patients attending a genetic counselling clinic. In all 13 patients, the placenta was anterior or fundal in position. By allowing for a rise in serum AFP levels of 4 μg/l for each fetal cell seen in 30 high power fields (Kleihauer test), a 62·5 per cent reduction in the number of patients selected for amniocentesis because of raised serum AFP levels would have been achieved. The occurrence of fetomaternal haemorrhages at the time of amniocentesis can be detected by either the Kleihauer technique or the measurement of maternal serum AFP levels.

ALTHOUGH the screening of maternal serum alpha-fetoprotein (AFP) levels for the antenatal diagnosis of neural tube defects (NTDs) is likely to become a routine part of obstetric practice, as many as 30 per cent (Ferguson-Smith *et al*, 1978) to 90 per cent (U.K. Collaborative Study, 1977) of women with raised serum AFP levels have normal fetuses. Raised AFP levels due to mistaken gestational age, multiple pregnancy or missed abortion can be excluded by ultrasound examination. Even so, as many as 0·5 per cent of pregnant women could have an unnecessary amniocentesis, a procedure not without risk.

In a recent study we found an association between spontaneous fetomaternal haemorrhage and raised maternal serum AFP levels before amniocentesis. The present study analyses this association in some detail.

PATIENTS AND METHODS

One hundred and fifty patients referred to the Genetic Counselling Clinic of the Royal Women's Hospital for diagnostic amniocentesis form the basis of this study. The indications for amniocentesis included a maternal age of over 40 years or a previous history of fetal NTD or chromosomal abnormality. The mean gestational age at the time of amniocentesis was 15 weeks (range 14 to 20 weeks). All patients had an ultrasound examination just before amniocentesis to confirm the gestational age, exclude multiple pregnancy and locate the placenta, but the presence or absence of vaginal bleeding prior to amniocentesis was unfortunately not recorded. All of the patients in the study had singleton pregnancies and were ultimately delivered of normal healthy children.

Venous blood samples were collected immediately before and five minutes after amniocentesis and in 33 patients a further sample was collected 30 minutes later.

Fetal cells in the maternal blood were identified by the Kleihauer technique. A 10 per cent suspension in Rous-Turner solution was used for making blood smears; these were dried for 15 minutes at room temperature, then fixed in 80 per cent ethanol for 5 minutes and dried at 37°C for 15 minutes. The adult cells were eluted at 37°C for 5 minutes in Kleihauer buffer (0·75 g disodium hydrogen orthophosphate, 1·54 g citric acid in 100 ml of distilled water, pH 3·3), stained with Harris haematoxylin solution (80 per cent), washed and counter-stained with 1 per cent aqueous eosin stain for 30 to 60 seconds. A total of 30 high power fields was examined on each slide. Ten fetal cells per 30 high power fields was considered equivalent to a fetal bleed of 1 ml, but less than 5 fetal cells per 30 high power fields was considered to be doubtful evidence of fetomaternal haemorrhage.

AFP was estimated using an Abbot double antibody radioimmunoassay kit. A 100 μl volume of serum was incubated for 32 hours at 4°C with 100 μl of ^{125}I-labelled AFP (specific activity 0·5 μCi/μg), 100 μl of borate buffer (pH 8·6, 0·1 mmol/l in 0·5 per cent bovine serum albumin) and 100 μl of anti-AFP serum (rabbit anti-human AFP, diluted 1:60 000). The Nishi AFP standard was diluted in borate buffer to give concentrations from 0 to 320 μg/l. All tubes were then incubated with 100 μl of goat anti-rabbit IgG for 12 hours at 4°C then, after the addition of 400 μl of dextran, incubated for a further 30 minutes. Following centrifugation at 3000 revolutions/minute for 30 minutes, the supernatant was discarded and the precipitate counted. At an AFP value of 30 μg/l, the intra- and inter-assay coefficients of variation were 4·5 per cent and 6·2 per cent respectively.

A significant fetomaternal haemorrhage due to amniocentesis was diagnosed if the post-amniocentesis serum AFP level was 40 per cent or more above the pre-amniocentesis level, or if the number of fetal red cells seen in 30 high power fields was increased by 5 or more.

One further patient had fetal cell counts and serum AFP level measurements for 34 days after fetomaternal haemorrhage at the time of delivery.

RESULTS

Of the 150 patients studied, 13 (8·7 per cent) were found to have elevated maternal serum AFP levels before amniocentesis (Fig. 1) and the

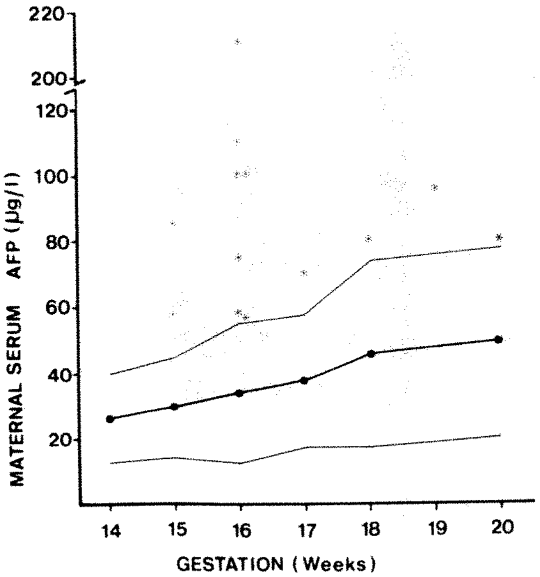

FIG. 1

Maternal serum AFP levels. The normal range is shown as the mean ± 2 SD in the patients with negative Kleihauer tests prior to amniocentesis. The individual values of the 13 patients found to have elevated levels are also shown.

TABLE I

Patients with elevated maternal serum AFP levels and fetal cells before amniocentesis

			Maternal serum AFP (μg/l)		No. of fetal cells/30 HPF	
Patient No.	Gestation (weeks)	Placental site	Before amniocentesis	After amniocentesis	Before amniocentesis	After amniocentesis
1	15	Fundal	85	85	13	16
2	15	Anterior	58	90	5	11
3	16	Anterior	210	210	43	33
4	16	Anterior	110	110	10	9
5	16	Anterior	100	100	8	6
6	16	Anterior	100	100	5	7
7	16	Anterior	75	75	5	5
8	16	Anterior	58	60	3	2
9	16	Anterior	56	56	3	3
10	17	Anterior	70	70	++	++
11	18	Fundal	80	80	10	10
12	19	Anterior	95	100	18	21
13	20	Anterior	80	80	++	++

++ Fetal cells detected but not counted.

blood of 11 of these subjects also contained fetal cells before amniocentesis (Table I). Following amniocentesis only patient No. 2 showed evidence of a further fetomaternal haemorrhage, although the placenta was anterior or fundal in all patients. Amniotic fluid AFP levels in these 13 patients were all normal.

The remaining 137 patients had normal maternal serum AFP levels, negative Kleihauer tests before amniocentesis, and normal amniotic fluid AFP levels. Following amniocentesis, 14 patients (10·2 per cent) had an increase in maternal serum AFP levels but only 11 of these patients showed a significant increase in fetal cells (Table II). In none of the patients who had blood samples taken at 5 and 30 minutes after amniocentesis did fetal cells appear for the first time at 30 minutes. Thirteen of the 14 patients had anterior placentae and clear amniotic fluid was obtained from all of them. Although a positive correlation was found between the rise in maternal serum AFP levels and the number of fetal red cells detected ($r = 0 \cdot 8$), the increase in maternal serum AFP after amniocentesis ranged from 2 μg/l for each fetal cell seen in 30 high power fields (Patient No. 4) to 10·8 μg/l for each fetal cell seen in 30 high power fields (Patient No. 9). All except two patients showed an increase in serum AFP of at least 4 μg/l for each fetal cell seen in 30 high power fields and the mean increase was 7·2 μg/l for each fetal cell seen in 30 fields.

We followed the serum AFP and the number of fetal cells in a patient with a large fetomaternal haemorrhage at about the time of delivery. Mrs. J.G., a primigravida, group A rhesus negative, presented in early labour at 38 weeks gestation after an uneventful pregnancy. The fetal heart could not be heard at the time of admission and a stillborn female infant weighing 2250 g was delivered 17 hours later. The infant, group 0 rhesus negative, was extremely pale at birth. Post mortem examination showed the cause of fetal death to be intrauterine hypoxia, however, there had been no intrapartum haemorrhage and the placenta appeared normal. A large fetomaternal haemorrhage was presumed and this was confirmed on Kleihauer testing and

TABLE II
Patients with significant fetomaternal haemorrhage after amniocentesis

Patient No.	Gestation (weeks)	Placental site	Maternal serum AFP (μg/l)		No. of fetal cells/30 HPF	
			Before amniocentesis	5 minutes after amniocentesis	Before amniocentesis	5 minutes after amniocentesis
1	17	Anterior	40	920	0	84
2	16	Anterior	48	600	0	75
3	16	Anterior	38	210	0	16
4	16	Anterior	30	60	2	15
5	16	Anterior	27	125	1	14
6	16	Anterior	27	87	2	16
7	16	Anterior	28	70	1	10
8	16	Anterior	25	88	0	8
9	18	Posterior	37	145	0	10
10	18	Anterior	20	120	0	10
11	16	Anterior	48	80	0	10
12	16	Anterior	27	40	0	3
13	16	Anterior	38	55	0	4
14	16	Anterior	28	44	0	3

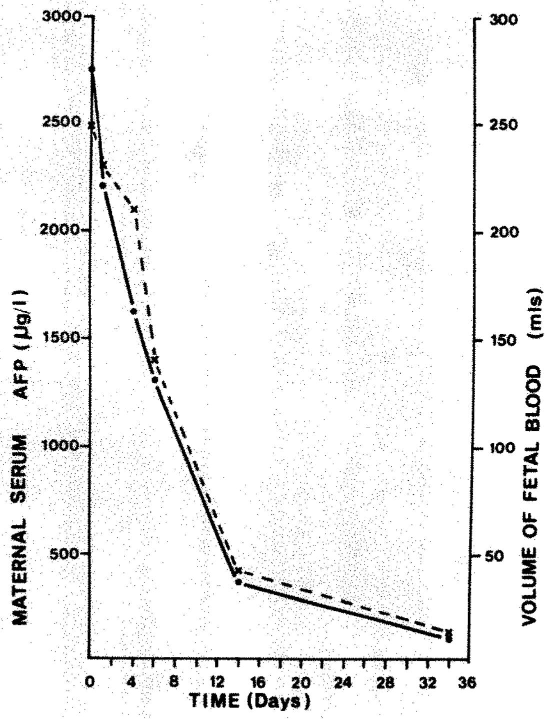

FIG. 2
Disappearance of AFP and fetal cells from the circulation of patient studied for 34 days after a significant fetomaternal haemorrhage at the time of delivery at term. ×————× volume of fetal blood estimated by the Kleihauer technique. ●————● serum AFP levels.

the finding of a grossly elevated maternal serum AFP level. Subsequent disappearance rates of fetal cells and AFP were identical (Fig. 2).

DISCUSSION

We confirm the usefulness of measuring AFP levels for the detection of fetomaternal haemorrhage after amniocentesis (Horacek *et al*, 1976; Lachman *et al*, 1977) and note that a clear tap is no guarantee against fetomaternal haemorrhage. We also confirm the need to obtain maternal blood for fetal cell counts in patients with raised serum AFP levels.

Thirteen patients in this study had raised maternal serum AFP levels before amniocentesis and in 11 of them fetal cells were detected by the Kleihauer test on maternal blood. Thus the wide range of maternal serum AFP levels in normal pregnancy reported in the literature may be due to the presence of fetal blood in the maternal circulation and this point should be given due consideration when selecting patients for amniocentesis.

By allowing a rise in maternal serum AFP of 4 μg/l for each fetal cell seen in 30 high power fields, unnecessary amniocenteses could be avoided. In our series only three of the eight patients with significant fetomaternal haemorrhages had serum AFP levels which would still have been above the normal range after correcting for the presence of fetal cells.

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We thank the Consultant Medical Staff of the Hospital for referring patients under their care.

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A COMPARISON OF CROWN-RUMP LENGTH MEASUREMENTS USING A REAL-TIME SCANNER IN AN ANTENATAL CLINIC AND A CONVENTIONAL B-SCANNER

BY

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Summary

In a series of 168 patients in the first trimester of pregnancy, fetal crown-rump length (CRL) measurements were attempted in the Antenatal Clinic using a linear-array real-time ultrasound scanner. The measurements could not be made in 23 of the patients; most of them had a gestational age of less than 10 weeks and the difficulty in obtaining measurements was usually due to an underfilled maternal bladder. When compared with CRL measurements obtained with a conventional B-scanner, a good correlation was obtained ($r = 0 \cdot 92$); 80 per cent of the 'real-time' values fell within a range of ±5 mm of the conventional values. In all patients the estimates of gestational age using the two methods were within one week of each other.

IN a previous communication we showed that fetal biparietal diameter (BPD) measurements, performed by an experienced operator using a linear-array real-time scanner, compared favourably with those using a conventional B-scanner (Adam *et al*, 1978). The small additional error incurred with the real-time scanner was considered to be acceptable if the measurement was used for the purposes of estimating gestational age up to the 28th week.

Many patients first attend the antenatal clinic before BPD measurements are reliable (before 12 weeks), and measurement of the fetal crown-rump length (CRL) during the first trimester is a very accurate method of gestational ageing (Robinson, 1973; Robinson and Fleming, 1975; Drumm *et al*, 1976). Therefore it seemed logical to extend our study to include an assessment of the feasibility and accuracy of real-time scanner measurements at this stage of pregnancy.

EQUIPMENT

The real time scanner used in this study was a Diagnostic Sonar System 85 (Diagnostic Sonar Ltd., Livingston, Scotland), with a 3·5 MHz linear array transducer. Its adjustable calipers could be moved independently over the surface of the screen (Fig. 1) obviating the need to orientate the transducer to be at right angles to the desired measurement plane. They had been modified so that their assumed calibration

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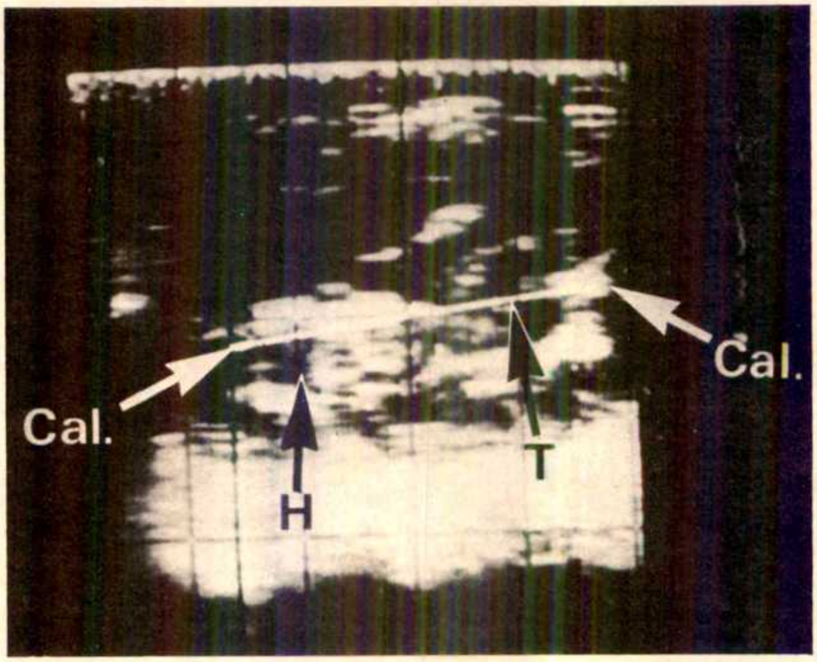

FIG. 1

Twelve week gestation fetus. Cal—Caliper dots: H—Head; T—Trunk.

velocity was 1540 ms^{-1} in the variable position mode rather than the standard 1600 ms^{-1} calibration.

PATIENTS AND METHODS

One hundred and sixty-eight consecutive patients, who were thought to be in the first trimester of pregnancy at their initial visit, were included in the study. Two operators performed the majority of the measurements—a sister midwife trained in the use of the real-time scanner, and an obstetrician experienced in the use of both equipments.

The ultrasonic examinations using the real-time scanner were undertaken, without prior patient preparation, immediately after the clinical examinations. Thus, since the patients voided urine before being seen by the clinician, only a small minority had even partially filled bladders.

Fetal measurement was made by an adaptation of the technique described by Robinson (1973). The longitudinal lie of the fetus was defined, and the caliper dots were moved to either end of the fetal echo complex. The procedure was repeated to ensure that the longest length of fetal echoes, the crown-rump length (CRL) had been obtained, and the measurement was then read from the digital display. Following this, the patient was asked to fill her bladder, and a conventional CRL measurement was then obtained with the Diasonograph NE 4102 (Robinson, 1973).

The operators assessed their measurements as 'good', 'fair' or 'poor' according to the ease of measurement, the amount of fetal movement, the definition of the fetal crown and rump, and the presence or absence of excessive fetal flexion.

RESULTS

The number of patients at each week of gestational age, together with the success rates in obtaining CRL measurements with the real-time scanner, is shown in Table I. No measurement was possible in 23 patients (14 per cent), due mainly to the problems encountered as a result of an underfilled bladder. No reliable measurements of fetuses smaller than 8 weeks size were obtained, and in the 8 to 9 week range a satisfactory measurement was achieved in only 6 of 20 patients.

The distribution of differences between the real-time and conventional B-scan measurements for the remaining 145 patients is shown in Figure 2. In 80 per cent of patients the real-time CRL measurements were within 5 mm of the 'conventional' CRL values; in only one patient, in whom the real-time measurement was 'poor', was the difference greater than 8 mm. A statistical analysis showed that the two sets of measurements were highly correlated (r = 0·92) and this close comparability held throughout the gestational age range studied.

TABLE I

Success of crown-rump length (CRL) measurement

Gestational age (weeks)	Number of patients	Number in which measurement of CRL obtained
8–9	20	14
10	29	21
11	29	27
12	40	38
13	40	37
14	10	8

A comparison was also made of the real-time CRL measurements and the 'expected CRL values' (based on the values published by Robinson and Fleming, 1975) in a subgroup of 72 patients whose menstrual data were considered to be reliable. Eighty-one per cent of the measurements were within 5 mm of the expected values, and all were within 8 mm (r = 0·95).

DISCUSSION

Measurement of the fetal CRL is one of the most accurate ancillary methods of estimating gestational age (Robinson, 1973; Robinson and Fleming, 1975; Drumm *et al*, 1976). Whereas in this study CRL measurements could be obtained in only 4 out of 5 patients, using a real-time scanner in the antenatal clinic, it should be

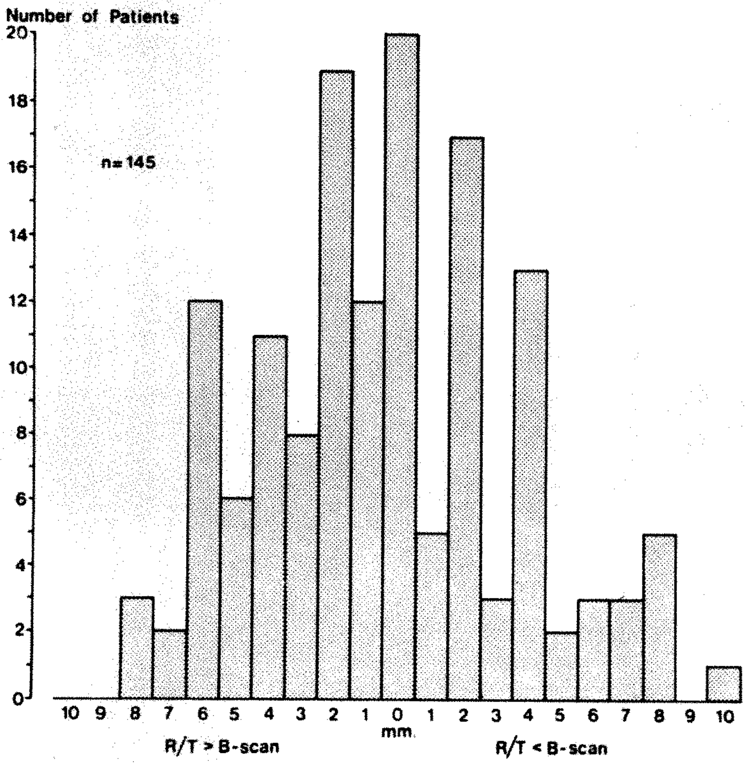

FIG. 2

Comparison between the real-time and the conventional B-scan CRL measurements.

stressed that few patients had an adequately filled bladder. Thus the incidence of difficulties with measurement increased the earlier a pregnancy was scanned (Table I). No reliable measurements were possible in pregnancies of less than eight weeks. However, as we intended to evaluate the use of a real-time scanner in a busy routine antenatal clinic, an assessment of measurements made in this way was valid on a practical basis. Despite the inequality of patient preparation, the measurements that could be made with the real-time scanner compared well with the conventional B-scanner measurement obtained under optimal conditions (r = 0·92). In practical terms, the gestational ages determined from the real-time and conventional B-scan measurements were within one week of each other in every case.

While the resolution capabilities of linear-array real-time scanners are inherently poorer than those of conventional B-scanners, the former equipment has the advantages that fetal movements are more readily appreciated, and that the transducer can be more easily realigned along the long axis of the fetus in the event of such movements.

Although scanning difficulties are often encountered before 10 weeks of pregnancy, fetal CRL measurements made with a real-time scanner are sufficiently accurate for assessing gestational age. When there are scanning problems the patient must be referred for an examination using conventional equipment and under more ideal conditions.

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THE ACCURACY OF RADIOLOGICAL ESTIMATES OF GESTATIONAL AGE USING EARLY FETAL CROWN-RUMP LENGTH MEASUREMENTS BY ULTRASOUND AS A BASIS FOR COMPARISON

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Summary

Radiological estimates of gestational age in late pregnancy were compared with the gestational ages based on first trimester ultrasound crown-rump length measurements in a series of 125 patients. It was found that the 95 per cent confidence limits of a radiological estimate were ± 3½ weeks, that both distal femoral and upper tibial epiphyses were frequently present much earlier than 36 and 38 weeks respectively, and that in almost half of the growth-retarded babies in the series there was a bone-age discrepancy of three or more weeks. It is recommended that more liberal use is made of early ultrasound measurements for the assessment of gestational age.

AN accurate knowledge of gestational age is required for the optimal management of a pregnancy. In this context, diagnostic ultrasound has been found to be an extremely useful ancilliary aid, particularly in the first trimester where an estimate can be given to within ± 4 days using a crown-rump length (CRL) measurement (Robinson, 1973; Robinson and Fleming, 1975; Drumm, 1977). However, despite the increasing use of ultrasound, radiological techniques are still widely employed especially in those hospitals where ultrasound facilities are not readily available.

While much has been written on the radiological assessment of gestational age, the predictive accuracy of this method has hitherto been related to such variables as the dates of the last menstrual period and the first appreciation of fetal movements as recollected by the patient, clinical estimates of uterine and fetal size, and the date of onset of spontaneous labour (Hartley, 1957; Schreiber *et al*, 1963; Russell 1969 and 1973).

Since each of these are themselves subject to appreciable error and variation, we considered that more reliable data on the accuracy of radiological techniques would be obtained if gestational age was based on a more exact reference point, such as a first trimester CRL measurement.

METHODS

During the years 1971 to 1975 at the Queen Mother's Hospital, Glasgow, 125 patients with singleton pregnancies had both an ultrasound examination in the first trimester (including a CRL measurement) and a radiological examination in the third trimester. The major indications for the latter procedure included: the estimation of gestational age; 'exclusion' of fetal abnormality; antepartum haemorrhage; and suspected cephalopelvic disproportion in labour.

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TABLE I

Radiological criteria employed for assessing gestational age

	Gestational Age (weeks)
Ossification centres	
Distal femoral epiphysis	36
Proximal tibial epiphysis	38
Femoral and tibial epiphyses equal in size	40
Tibial centre larger than femoral	40 +
Fat line	32
Subjective indices	
Thickness of fat line	
Degree of skull and spinal ossification	

The CRL measurement technique employed was that described by Robinson (1973), and all measurements were performed by the same operator (HPR). The X-ray films were reviewed by one of us (EMS) on a blind basis, that is in the absence of any clinical data. Predictions of gestational age were made in the following way: using the criteria detailed in Table I the films were first divided into age-groupings of two weeks (30–32, 32–34 etc.), and each film was then allocated a more exact value; the films allocated to the same week were re-examined as a group, and age assessments were finalized.

The ultrasound 'CRL age' of each pregnancy at the time of the respective radiological examinations was determined, and comparisons then made of the resulting pairs of estimates.

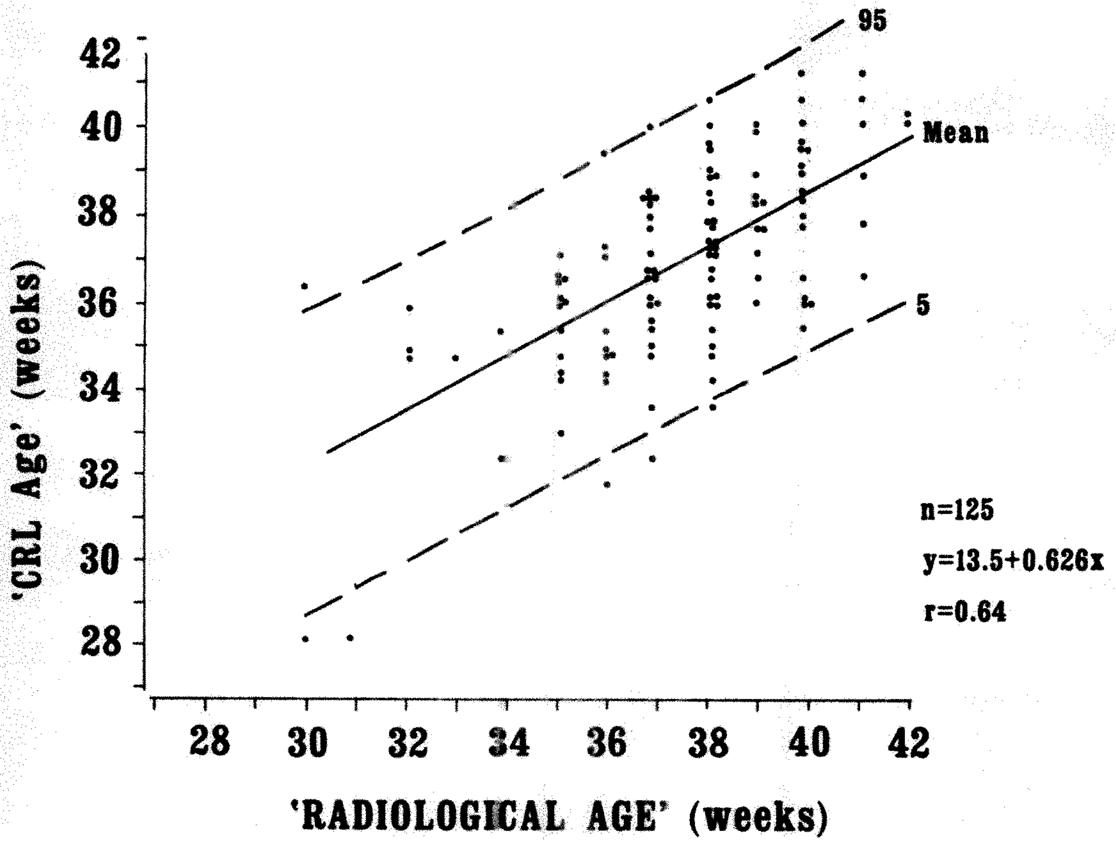

FIG. 1

A least squares regression analysis and 95 per cent confidence limits of 'CRL age' against radiological estimates in 125 pregnancies.

RESULTS

In Figure 1, the ultrasound estimates of gestational age were plotted against the radiological estimates, and a least regression analysis was performed to obtain the mean line and the 95 per cent confidence limits for the population. Variance ratio analysis of the data showed that the use of a straight line was valid. The mean line was described by the equation $y = 13{\cdot}5 + 0{\cdot}626x$. Thus, for a given radiological estimate, the 95 per cent confidence limits of gestational age (based on an early CRL measurement) were ± 3½ weeks.

The data were further analysed to determine the proportion of pregnancies, at each week of gestational age (CRL age), in which distal femoral and upper tibial epiphyses had been demonstrated. The results are shown in Figure 2.

Of the 12 babies in this study whose weights were below the tenth centile (Lubchenco *et al*, 1963) at delivery, the antenatal radiological estimate of age was three or more weeks less than the 'CRL age' in five (42 per cent); the remainder were within two weeks.

DISCUSSION

Previous studies have shown that a CRL measurement in early pregnancy provides a very accurate means of estimating gestational age (Robinson, 1973; Robinson and Fleming, 1975; Drumm, 1977). In contrast, the results of this investigation have shown that a radiological assessment of gestational age in late pregnancy provides an accuracy of no better than ± 3½ weeks. These limits were constant over the period 30 to 42 weeks. Russell (1969), however, in his study of 3606 pregnancies found that the 2SD limits of the error of a radiological prediction of fetal age fell from ± 54 days when the pregnancy was less than 31 weeks, to ± 20 days between 38 weeks and term. The difference between the two studies may be due simply to the small numbers of patients in the current investigation who were at less than 35 weeks.

Of the 25 patients examined radiologically at 36 weeks (CRL age), a distal femoral epiphyseal (DFE) centre was identified in 20 (80 per cent). While this figure is lower than the 96 per cent quoted by Schreiber *et al* (1963), both studies would appear to suggest that the presence of a DFE is good evidence that a fetus has an age of 36 weeks or over. However, analysis of the data in this way is misleading since it gives no indication about the number of pregnancies at less than 36 weeks in which the DFE is also present. Such information is important if radiological findings

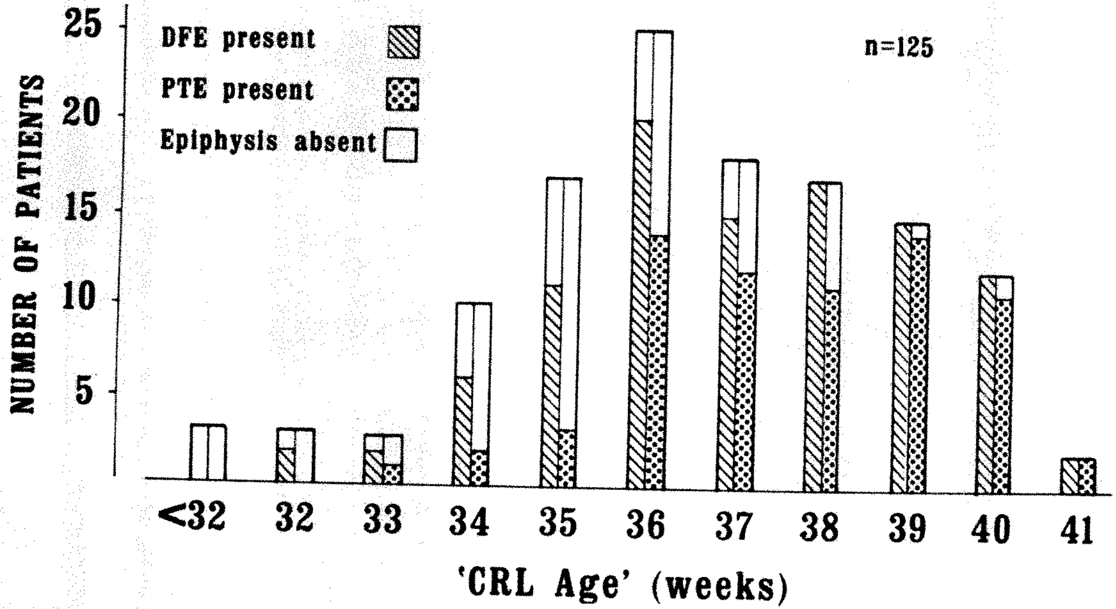

FIG. 2

Distribution of the presence or absence of distal femoral (DFE) and proximal tibial (PTE) epiphyses in the 125 fetuses.

are to be used in the prospective management of a pregnancy.

In this context Schreiber *et al* (1963) found DFEs to be present in the antenatal films of over two-thirds of the babies who were 'premature' by birth weight. There were comparable findings in the current study where a DFE was present in no less than 21 of 36 pregnancies (58 per cent) which were at less than 36 weeks CRL age. Similarly, a proximal tibial epiphysis (PTE) was present in 32 of 79 pregnancies (41 per cent) which were at less than 38 weeks CRL age. Therefore, too much reliance should not be placed on the presence of these radiological features when planning an elective induction of labour. A further factor which may contribute to an error in the radiological estimation of gestational age is the possibility that the fetal bone age may be retarded due to intrauterine fetal growth retardation (Scott and Usher, 1964; Murphy, 1969; Croall and Grech, 1970). These observations are supported by the findings in this study where 42 per cent of the growth-retarded fetuses had a 'bone age' three or more weeks less advanced than CRL age.

In view of the small but important risk of antenatal fetal radiography, and the demonstrated inaccuracy of radiological methods of assessing gestational age in this and other studies, it is suggested that exposure of a fetus for this purpose is rarely justifiable. The major possible exception is the patient who first attends very late in pregnancy and whose dates are uncertain, and who, for pressing medical or obstetrical reasons, requires to be delivered electively.

It is recommended that more liberal use is made of the more reliable ultrasound techniques with the ideal of screening every patient at the time of her first antenatal clinic visit.

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ROUTINE INDUCTION OF LABOUR WITH EXTRA-AMNIOTIC PROSTAGLANDIN E_2 IN A VISCOUS GEL

BY

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Summary

Prostaglandin E_2, 350 μg dispersed in a viscous gel, tylose, was introduced into the extra-amniotic space as a single dose in 285 patients to induce labour. With a favourable cervix, 82 per cent of multiparae and 50 per cent of primiparae were successfully induced. With unfavourable induction features, the success rates were 48 per cent and 24 per cent respectively. In the remaining patients, all but four were successfully delivered when intravenous oxytocin was also used. The method was safe, simple and inexpensive and had many advantages for patients and nursing staff.

PROSTAGLANDINS have been used intravenously (Beazley and Gillespie, 1971; Craft *et al*, 1971) and orally (Karim and Sharma, 1971; Craft, 1972; Kelly *et al*, 1973; Wilkin *et al*, 1976) to induce labour. However, side effects such as nausea vomiting and diarrhoea are relatively common, especially if large doses are required. The use of prostaglandins to ripen the cervix prior to induction, by infusion into the extra-amniotic space, was described by Calder *et al* (1974). MacKenzie and Embrey (1976) first used tylose gel as a vehicle for a single application for induction of mid-trimester abortions. The same technique has been used successfully to ripen the unfavourable cervix before induction of labour (Shepherd *et al*, 1976; Calder *et al*, 1977; Thiery *et al*, 1977) and to induce labour in patients with favourable induction features (Mellows *et al*, 1977). This paper reports the use of this technique for routine induction of labour whatever the induction features.

PATIENTS AND METHODS

There were 285 patients who were unselected and required induction of labour. The indications for induction are given in Table I. There were 139 primiparae and 146 multiparae. The gestational age at induction ranged from 34 to 43 weeks (by menstrual dates or ultrasound cephalometry). In all patients, the fetal presentation was cephalic and there were no multiple pregnancies. There were 217 patients with a favourable cervix (Bishop score 5–13; Bishop, 1964) and 68 patients with a score of 0 to 4. Four patients had been

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TABLE I

Indications for induction of labour

	Primiparae		Multiparae	
Indication	No.	per cent	No.	per cent
Post-dates	76	55	60	41
Hypertension	39	28	43	30
Placental insufficiency	14	10	12	8
Poor obstetric history	5	3·5	12	8
Miscellaneous—diabetes, rhesus, social, geographic	5	3·5	19	13
Total	139		146	

delivered previously by lower segment Caesarean section.

The prostaglandin E_2 (PGE_2) gel was prepared aseptically by the hospital pharmacist. Methyl-ethyl-hydroxycellulose powder (Tylose MH300p, Hoechst) was sterilized by autoclaving and incorporated into a sterile solution of PGE_2 in normal saline. A gel was obtained of tylose 5·5 per cent which contained 350 μg in 7 ml of gel. Radioimmunoassay has shown that the gel retains over 90 per cent potency for at least four days when stored at 4°C and eight weeks at −20°C.

The procedure was explained to the patient and 7 ml of tylose gel containing 350 μg of PGE_2 was transferred to a sterile disposable syringe. A disposable urethral catheter 12FG was attached firmly to the syringe and filled with gel to eliminate air. With aseptic precautions, the catheter was introduced through the cervix until between 5 and 10 cm were in the extra-amniotic space. Gel was then injected and the dead space cleared with air. After resting for 20 minutes, the patient was allowed up and about. In some patients with a very unfavourable cervix, the catheter was introduced under direct vision using a Cuscoe's speculum.

The onset of labour was usually slowly progressive, beginning with low back ache followed by uterine contractions similar to the onset of spontaneous labour. When labour was established, the membranes were ruptured and internal monitoring instituted. If regular contractions were not established within four to six hours, amniotomy was done and intravenous oxytocin started if necessary after a delay of 30 minutes.

RESULTS

Patients were allocated to four groups (A to D) according to the Bishop score and the need or not for intravenous oxytocin. Patients in group A, with a favourable cervix, and group B, with an unfavourable cervix, went into labour successfully and did not need intravenous oxytocin. Patients in group C, favourable cervix, and Group D, with an unfavourable cervix, required intravenous oxytocin because of an unsatisfactory or absent response to prostaglandin.

The details and results of primiparous patients are shown in Table II. The mean Bishop score was only slightly less in patients in groups C and D compared with A and B but the response to PGE_2 alone was poor. The mean interval between induction and the onset of labour in groups A and B was four hours. The mean duration of labour was longer in patients with an unfavourable cervix and in whom oxytocin was required. The overall epidural rate was 81 per cent and forceps deliveries were required for 60 per cent of patients.

The details and results for multiparous patients are given in Table III. The mean Bishop score was very similar in the comparable groups A and C and in groups B and D, despite the different response to extra-amniotic PGE_2. The mean interval between induction and the onset of labour was only three hours. The mean duration of labour was related to Bishop score and the need for supplementary oxytocin. The epidural rate was 56 per cent and the forceps delivery rate 17 per cent.

Eight patients (2·8 per cent), seven primiparae and one multipara, required delivery by Caesarean section. In three patients there were significant variations in fetal heart rate; one of them had normal contractions but a small-for-dates baby; one had epidural-induced hypotension; and the third an increasing tachycardia at 6 cm dilatation of the cervix after 16 hours of labour. In one patient, Caesarean section was required at full cervical dilatation because of

TABLE II

Distribution of patients and results in 139 primiparae related to Bishop score and method required to achieve delivery

Group	Patients		Bishop score		Gestational age (weeks)		Method	Failed induction	Mean duration of labour (hours)
	No.	per cent	Range	Mean	Range	Mean			
A	51	37	5–13	6·8	37–42	40·6	PGE_2	0	8
B	9	6	0–4	3·3	34·5–42	40·5	PGE_2	0	9
C	51	37	5–13	6·3	38·5–42	40·6	PGE_2 + oxytocin	0	10¾
D	28	20	0–4	2·8	36–42	40·3	PGE_2 + oxytocin	4	13¼

TABLE III

Distribution of patients and results in 146 multiparae related to Bishop score and method required to achieve delivery

Group	Patients		Bishop score		Gestational age (weeks)		Method	Failed induction	Mean duration of labour (hours)
	No.	per cent	Range	Mean	Range	Mean			
A	94	65	5–13	6·7	37–43	40·5	PGE_2	0	4½
B	15	10	0–4	3·3	34·5–42	40·0	PGE_2	0	7
C	21	14	5–13	6·4	34–42	39·6	PGE_2 + oxytocin	0	7¼
D	16	11	0–4	3·1	37–42	40·0	PGE_2 + oxytocin	0	9

cephalopelvic disproportion. The remaining four patients failed to go into labour despite prostaglandins and high doses of oxytocin. All four were primiparae with a Bishop score of 2 or less.

There were 285 infants delivered and 276 (97 per cent) had an Apgar score of 8 or more at five minutes. There were four infants with a score of 6 and five with a score of 7; all responded well to resuscitation.

There were very few maternal problems. Antepartum haemorrhage or inadvertent rupture of the membranes did not occur. Twelve patients noted shivering with contractions before epidural analgesia. There were occasional transient episodes of increased uterine baseline tone which resolved spontaneously without causing fetal distress. No patient suffered nausea vomiting or diarrhoea. During labour, 35 patients (12 per cent) developed a pyrexia of 38°C or more without evidence of bacteriological infection. This pyrexia was attributed to the thermogenic effect of prostaglandins (Dingfelder and Brenner, 1978).

DISCUSSION

The use of a single application of PGE_2 locally to induce labour has many advantages. The patient is not restricted to bed and appreciates the freedom to move around and the gradual onset of labour. Midwives are released from the need to supervise equipment and intravenous infusion immediately after induction, and the need for expensive infusion pumps is reduced. The equipment is simple and inexpensive. The method appears to be remarkably safe and overstimulation of the uterus has not occurred, even with doses up to 1000 μg used to induce labour in patients with intrauterine fetal death.

The incidence of failed induction is low, so the need for Caesarean section reduced. In a five-month survey of induction of labour in this hospital by amniotomy and intravenous oxytoxin (Tivey-Jones and Malvern, 1975, personal communication), 8 of 19 primiparae (42 per cent) with a Bishop score of 0 to 3 failed to labour and required Caesarean section. In this series, 4 of 22 patients (18 per cent) with a Bishop score of 0 to 3 required delivery by Caesarean section because of failure to go into labour. In patients with a low Bishop score, it is now our practise to administer the PGE_2 the evening before planned induction to ripen the cervix, and to give the induction dose the next morning. With experience, the dose has been increased to 500 μg according to cervical status.

The main drawback of this technique of induction is that the outcome is unpredictable, and some patients do not respond to PGE_2 even if the cervix is favourable. This technique is not suitable for patients with a low-lying placenta, nor in patients with a cervical dilation of 4 cm or more because PGE_2 may then cause hypertonic contractions.

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NORMAL AND ABNORMAL ANTENATAL ULTRASONIC CARDIOGRAPHIC PATTERNS

BY

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Summary

Data is presented from 1019 antenatal ultrasonic cardiographs performed on 391 patients; uterine contractions were not monitored concurrently with the fetal heart rate (FHR). No fetal deaths *in utero* or preterminal FHR patterns were seen within 24 hours of a normal trace. A comprehensive classification of FHR patterns is presented.

STRESSED and non-stressed antenatal cardiotocographs are now accepted methods of monitoring fetal well-being. The proponents of non-stressed cardiotocography come mainly from Europe and Great Britain (Kubli *et al*, 1977; Visser and Huisjes, 1977; Flynn and Kelly, 1977) whereas American authors have made a strong case for the oxytocin challenge test (Freeman, 1975; Freeman *et al*, 1976; Farahani *et al*, 1976; Garite *et al*, 1978). Correct interpretation of normal and abnormal fetal heart rate (FHR) patterns is of vital importance and a number of classifications and scoring systems have been devised (Rochard *et al*, 1976; Kubli *et al*, 1977; Visser and Huisjes, 1977; Pearson and Weaver, 1978). Just as electronic intrapartum monitoring can virtually eradicate intrapartum stillbirths (Beard, 1977), advocates of antenatal cardiotocography believe that many fetal deaths *in utero* can also be avoided. This study illustrates that the correct interpretation of antenatal FHR patterns provides enough information to manage most pregnancies which are at risk.

PATIENTS AND METHODS

Three hundred and ninety one at-risk antenatal inpatients provided 1019 ultrasonic cardiographic traces for analysis. The study extended from March 1978 to January 1979. Recordings were made using Sonicaid FM2 and FM3 monitors at a paper speed of 1 cm/minute. The patient lay comfortably in her bed; no emphasis was put on exact positioning, unless the patient was symptomatically affected by supine hypotension or if an abnormal-looking trace was obtained in which case the patient was placed in the lateral recumbent position. Traces were recorded for at least 20 minutes and only accepted for analysis if technically adequate. If there were doubts as to the normality of the record obtained, it was extended to 40 minutes or more, or else repeated within a few hours. The uterine contractions were not monitored concurrently. The classification of the FHR patterns is shown in Table I. Some of the patterns were adapted from other workers (Emmen *et al*, 1975; Rochard *et al*, 1976; Visser and Huisjes, 1977; Trimbos and Keirse, 1977; Wheeler and Murrills, 1978) and others were from the author's observations. Apart from clinical findings, other methods used for monitoring fetal welfare included a fetal movement chart (Cardiff count-to-ten chart; Pearson and Weaver, 1976), serum human placental lactogen estimation, ultrasound B-scanning and amniocentesis for amniotic fluid palmitate levels.

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RESULTS

The distribution of the various patterns is shown in Table I; 995 traces (97·6 per cent) were normal. There were 24 abnormal traces (2·4 per cent): 16 preterminal, 7 flat and 1 sinusoidal. Two types of preterminal pattern were seen: one with very small decelerations and the other with deep wide decelerations. The primary indications for performing the test are shown in Table II. Of the 391 patients, two intrauterine fetal deaths occurred before the onset of labour in patients with a preterminal pattern that was not acted upon (patients 1 and 362, Table V).

The time interval from the last cardiograph to the day of spontaneous labour, elective induction or elective Caesarean section is shown in Table III. No fetal deaths *in utero* were seen within seven days of a normal trace. Three hundred and seventy four patients had normal traces only, leaving 17 patients with one or more abnormal traces; of the 374 'normals' (386

TABLE I

Fetal heart rate pattern

Pattern	Description	No.
Normal		
Normal	Baseline FHR 120–160 bpm Baseline variability 5–50 bpm	618
Large swings	Baseline FHR 120–160 bpm Baseline variability >50 bpm	255
Persistent tachycardia	Baseline FHR 160 bpm or greater Baseline variability >5 bpm	60
Rest-activity cycle	Baseline FHR 120–160 bpm Baseline variability <10 bpm for at least 15–20 minutes, reverting to other normal patterns	58
Non-repetitive deceleration	Baseline FHR 120–160 bpm Baseline variability >5 bpm One large deceleration >50 bpm	4
Abnormal		
Preterminal	Type A Flat trace with loss of baseline variability <5 bpm, associated with recurrent shallow decelerations Type B Recurrent large declerations >50 bpm	16
Flat	Flat trace with loss of baseline variability <5 bpm, no decelerations	7
Sinusoidal	Baseline FHR 120–160 bpm Loss of baseline variability <5 bpm Sinusoidal pattern—frequency 2–5 per minute —amplitude 5–10 bpm	1
Total		1019

FHR = fetal heart rate
bpm = beats per minute

TABLE II

Primary indication for antenatal cardiograph

Indication for testing	No.
Hypertensive disorders	102
Uncertain dates and postmaturity	66
Antepartum haemorrhage	32
Low serum human placental lactogen (less than 5th centile)	29
Suspected fetal growth retardation	21
Twin pregnancy	11
Anaemia (haemoglobin less than 10 g/dl)	9
Diabetes	9
Other	112
Total	391

TABLE III

Time from last cardiograph to delivery

Interval between last cardiograph and delivery (days)	No.
0	23
1	94
2	63
3	33
4	17
5	13
6	15
7	15
>7	115
Unrecorded	3
Total	391

TABLE IV

Normal antenatal cardiographs followed by delivery of an infant with a five-minute Apgar score of less than 7

Patient No.	Complications	Delivery	Birth weight (g)	Gestation (weeks)	Apgar scores at 1 and 5 minutes	Progress of baby
2	APH	Breech LSCS for delay in second stage	2630	39	2, 4	Did well
23	Hypertension, FGR	Breech LSCS for acute fetal distress	2170	39	4, 5	Died day 8, septicaemia
68	Hypertension	LSCS for acute fetal distress	2990	38	2, 3	Tension pneumothorax immediately—did well
88	Gestational diabetes	LSCS for no progress	3790	38	6, 6	Did well
134	Hydramnios, previous stillbirth	LSCS for acute fetal distress	2800	40	2, 2	Multiple abnormalities, died
178	Hypertension, unknown dates	LSCS for no progress	2980	—	4, 6	Did well
188	Severe pre-eclampsia, placenta praevia, transverse lie	Elective LSCS	3310	36	4, 5	Did well
205	Two previous LSCS, unknown dates	Elective LSCS	2800	—	5, 5	Did well
285	Unstable lie	LSCS for acute fetal distress	3510	39	3, 5	Did well
303	Ruptured membranes 38 weeks	LSCS for acute fetal distress	2760	40	6, 5	Did well
331	Threatened premature labour	SVD	850	28	4, 5	Did well
334	APH	SVD	2600	34	3, 6	Did well
376	APH	SVD	2490	36	4, 5	Did well
380	Hypertension, uncertain dates	SVD	2760	—	4, 6	Did well
391	APH, unstable lie	Elective LSCS	2600	39	3, 6	Did well

LSCS = lower segment Caesarean Section
APH = antepartum haemorrhage

SVD = spontaneous vertex delivery
FGR = fetal growth retardation

TABLE V

Clinical features of patients with preterminal cardiograph pattern

Patient No.	Complications	Gestational age (weeks)	No. of pre-terminal traces	Interval between first abnormal trace and delivery or fetal death (hours)	Amniotic fluid	Birth weight (g)	Birth weight (centile)	Comments
1	Moderate to severe pre-eclampsia, asthmatic	34	2	36	Meconium	1280	< 5th	Vaginal delivery, IUD
8	Hypertension, methyl-dopa therapy	34	1	24	Oligo-hydramnios	1550	< 5th	Elective LSCS. Apgar score 3 and 6, survived
30	Hypertension, methyl-dopa therapy, FGR	32	2	20	Meconium	1340	10th	Elective LSCS, survived
32	Placenta praevia, recurrent APH	28	2	12	Clear	2800	>95th	Emergency LSCS intrapartum stillbirth, grossly abnormal baby
55	Low HPL, FGR	39	1	72	Meconium	1870	< 5th	Vaginal delivery, intrapartum asphyxia. Apgar score 0 and 2, NND at 12 hours
177	Falling HPL	40	1	1	Clear	2650	< 5th	Emergency LSCS (fetal bradycardia following amniotomy). Apgar score 9 and 10, survived
196	FGR	38	2	2	Clear	1930	< 5th	Emergency LSCS (fetal bradycardia following amniotomy). Apgar score 7 and 9. Cleft palate, micrognathia, survived
215	Severe rhesus incompatibility	37	2	72	Yellow	2640	>10th	Elective LSCS, Apgar score 5 and 8, cord haemoglobin 5·8 g/dl NND at 12 hours (following exchange transfusion)
250	Hypertension, FGR	38	2	12	Meconium	1750	< 5th	Elective LSCS, Apgar score 4 and 7, survived
362	Low HPL, FGR, previous IUD	30	1	15	Meconium	820	< 5th	Vaginal delivery, IUD

LSCS = lower segment Caesarean section
FGR = fetal growth retardation
APH = antepartum haemorrhage

HPL = human placental lactogen
IUD = intrauterine fetal death
NND = neonatal death

TABLE VI

Clinical features of patients with flat traces

Patient No.	Complications	Gestational age (weeks)	No. of flat traces	Interval between first abnormal trace and delivery (hours)	Amniotic fluid	Birth weight (g)	Birth weight (centile)	Comments
176	Anaemia, recurrent APH, poor obs. history, valium sedation	38	1	48	Clear	3500	<50th	Elective LSCS, Apgar scores 8 and 10, survived
215	Severe rhesus incompatibility	37	1	72	Yellow	2640	>10th	Elective LSCS. Apgar scores 5 and 8, cord haemoglobin 5·8/dl NND at 12 hours
221	Severe pre-eclampsia, high dose phenobarbitone	35	1	5	Clear	1530	< 5th	Elective LSCS, Apgar scores 7 and 9, survived
248	41 week gestation	41	1	72	Clear	4190	>90th	Amniotomy, vaginal delivery. Apgar score 9 and 10, survived
250	Hypertension, FGR	38	2	12	Meconium	1750	<5th	Elective LSCS, Apgar scores 4 and 7, survived
270	Hypertension	38	1	12	Clear	4510	>95th	Amniotomy, vaginal delivery. Apgar scores 9 and 10, survived

APH = antepartum haemorrhage
NND = neonatal death

LSCS = lower segment Caesarean section
FGR = fetal growth retardation

babies), 15 babies (3·8 per cent) had 5 minute Apgar scores which were less than 7—the clinical features of these patients are shown in Table IV. One baby died of septicaemia on the eighth day, another died of congenital abnormalities and the other 13 did well.

The clinical features of the preterminal trace patients are summarised in Table V. There were 10 patients showing preterminal patterns; five deaths occurred in this group—four deaths were possibly avoidable (patients 1, 55, 215 and 362). Two patients with preterminal patterns had a normal trace four days and two days previously. Hence there were no fetal deaths *in utero* or the appearance of a preterminal trace within 24 hours of a normal trace. The time interval from the first appearance of a preterminal trace to antenatal fetal death (patients 1 and 362 Table V) or delivery of the baby varied from one hour to three days (Table V). There were no false positive preterminal traces; the mean weight of these babies was 1863 g (at a mean gestation of 35 weeks)—which is under the fifth centile for birth weight according to Thomson *et al* (1968).

There were six patients showing seven flat traces (Table VI); two patients (Nos. 215 and 250) in this group also had preterminal patterns; the former baby had a cord haemoglobin of 5·8 g/dl and died 12 hours after an exchange transfusion, and the latter had thick, fresh meconium at elective Caesarean section when it was noted that the cord was twisted four times round the neck. Two patients (Nos. 176 and 221) were on sedative therapy.

The sinusoidal pattern as described by Rochard *et al* (1976) and Kubli *et al* (1977) was seen in one patient; a true knot in the cord was found after a normal vaginal delivery, and the baby did well.

Eight of the 403 babies delivered (391 patients) died. There were two fetal deaths *in utero*; three were due to gross congenital abnormality (one intrapartum stillbirth, two neonatal deaths); one was due to severe intrapartum asphyxia (type II dips and meconium stained amniotic fluid) leading to a neonatal death; one was due to septicaemia and occurred on the eighth day; and one followed an exchange transfusion given for severe rhesus incompatibility. Five of the eight deaths occurred in babies showing a preterminal antenatal cardiograph. All patterns except the preterminal, flat and sinusoidal, indicated that the fetus was not in immediate danger.

DISCUSSION

Non-stressed cardiography is of great value in the management of problem patients. The fetus is apparently not at risk for at least 24 hours following a normal trace. An antenatal cardiograph can be done at any time of day or night and can be relied upon to assess fetal wellbeing accurately.

Table I shows the wide range of normal traces; it confirms the findings of other workers (Visser and Huisjes, 1977; Flynn and Kelly, 1977; Kubli *et al*, 1977) who have shown that a 'reactive' fetus will demonstrate a baseline variability greater than five beats per minute in association with frequent accelerations. The ability of the cardiovascular system of the fetus to vary the regularity as well as accelerate its fetal heart rate seems to indicate it is in no immediate danger. The subclassification into normal, large swings, persistent tachycardia, rest-activity cycle and non-repetitive decelerations defines specific observed patterns that have resulted in fetuses who survive at least until delivery, with 96·2 per cent of these babies having five-minute Apgar scores greater than 7, indicating that the quality of the survival was usually very good. Our observation of four non-repetitive deceleration patterns confirm the findings of Trimbos and Keirse (1977) that immediate delivery is not necessary in these cases; all the babies with this pattern in this series survived and did well.

The results in the preterminal pattern group agree with the findings of Emmen *et al* (1975), Visser and Huisjes (1977), Kubli *et al* (1977) and Flynn and Kelly (1977) in that they are of ominous significance, and warrant prompt elective Caesarean section.

Some claim that it is difficult to judge baseline variability when the fetal heart rate is being recorded from a wide-angled transducer. This is not my experience.

Fetal heart rate patterns seem to provide adequate data for clinical management and the concurrent recording of uterine activity seems to me to be unnecessary.

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THE BIOCHEMISTRY OF AMNIOTIC FLUID WITH POOR FETAL GROWTH

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Summary

Amniotic fluid from 79 European and Asian mothers at term was examined for those biochemical changes which in postnatal life are associated with slow growth, a poor diet or frank malnutrition. Amniotic fluid from normal pregnancies of both races contained proportionally less urea nitrogen, more uric acid nitrogen and α-amino nitrogen, and more free hydroxyproline than was found in urine from pregnant mothers and the newborn. Some of these differences may reflect a relative reduction in nutrient supply in late pregnancy while others are due to immaturity of various biochemical systems. These explanations do not account for all the differences. Compared to results in normal mothers, the Asian mothers with light-for-dates babies showed changes suggesting undernutrition (high amniotic fluid alkaline ribonuclease and α-amino nitrogen). The European mothers with light-for-dates babies had biochemical evidence of reduced growth (low amniotic fluid total hydroxyproline) but not evidence of undernutrition. Mothers with light-for-dates babies in both races had a high amniotic fluid uric acid nitrogen; the cause of this is uncertain. The biochemical measurements were significantly different in the mothers with light-for-dates babies and were a more accurate prediction of poor intrauterine growth than clinical criteria alone. Nevertheless, the overlap with normal pregnancies was so great as to limit the clinical usefulness of these measurements in the management of an individual pregnancy.

IN late pregnancy, when the fetal skin has become keratinised, fetal urine makes a substantial contribution to the composition of amniotic fluid (Lind and Billewicz, 1971). It would be expected, therefore, that in the same way as urine from infants and children reflects their nutritional state, amniotic fluid may indicate the nutritional state of the fetus.

When the dietary protein intake of a child is reduced, urinary nitrogen excretion falls. This reduction affects all components of the total urinary nitrogen but is most marked for urea, the urea nitrogen:total nitrogen ratio being reduced (Gadkar *et al*, 1963). As the child becomes malnourished, further changes in cellular nitrogen metabolism occur which are reflected in the serum and urine. The relative proportion of plasma non-essential amino acid is increased, resulting in an increased plasma ratio of non-essential to essential amino acid, and in an overflow amino-aciduria which gives an increased urinary α-amino nitrogen (Arroyave, 1970). Both serum and urinary activities of alkaline ribonuclease are elevated; this enzyme is raised in children with kwashiorkor (Sigulem *et al*, 1973), in adults with negative nitrogen balance (Albanese *et al*, 1971), and in the placentas of malnourished mothers (Velasco *et al*, 1975). A raised activity probably reflects a need to conserve nitrogen (Scott *et al*, 1978). Initially, in response to the poor diet, growth is diminished and the excretion of hydroxyproline falls (Whitehead, 1965). This probably reflects the slow turnover of tissue collagen. As the child becomes more severely malnourished, hydroxyproline excretion increases as collagen breakdown predominates.

Thus in childhood when the diet is poor and the growth velocity is reduced or stationary, the following changes are found: hydroxyproline excretion is reduced and so is the urinary urea nitrogen:total nitrogen ratio. As the situation deteriorates and frank malnutrition occurs, the total hydroxproline excretion becomes raised, the alkaline ribonuclease activity is increased, the urinary α-amino nitrogen is raised, whilst the urea nitrogen:total nitrogen ratio remains low.

This investigation was planned, therefore, to look at the levels of the various components of amniotic fluid nitrogen, hydroxyproline and alkaline ribonuclease both in relation to fetal growth and nutrition, and to assess their potential clinical value.

METHODS

Patients

The population served by the hospital is broadly an under-privileged inner city group. One-third are Asian births, mainly in Moslems from Pakistan and Bangladesh but also a few Hindus from India. For diet, apart from pork, Moslem women will eat meat and the Hindu women will not eat beef; particularly the Gujaratis are vegetarian.

Table I describes the mothers and babies in the study and all the mothers gave consent. Forty-five pregnancies (32 European and 13 Asian) were normal and the babies well grown. Twenty-two pregnancies (18 European and 4 Asian) were complicated by hypertension (diastolic blood pressure above 90 mm Hg) but resulted in well grown babies. Treatment of hypertension invariably consisted of bed rest and sedation with diazepam if necessary. Only one patient was treated with hypotensive agents. Twelve pregnancies (8 European and 4 Asian) ended in the delivery of light-for-dates babies, namely the birth weight was below the 10th centile for gestational age, sex, maternal height and parity (Thomson, *et al*, 1968). Babies with a weight centile above the 10th were regarded as well grown. The light for dates babies were small in all measurements as well as weight. The Asian babies were slightly smaller than the Europeans.

Amniotic fluid

Amniotic fluid was obtained at 79 term deliveries. Mostly samples were from induction by hindwater rupture with a Drew-Smythe catheter. Uncontaminated fluid was also obtained by forewater rupture, Caesarean section, or during labour either after spontaneous rupture of the membranes or when the membranes were ruptured to accelerate labour. Indications for induction included hypertension, postmaturity, failing placental function and borderline cephalopelvic disproportion. Five of the Asian mothers with uncomplicated pregnancies were induced for this last reason. Samples (20 ml) of amniotic fluid were centrifuged, the supernatant was filtered (Millipore filter, type SC, 8 μm), stored at —20°C and analysed for urea and creatinine nitrogen (standard Technicon methods), α-amino nitrogen (Goodwin, 1970), uric acid nitrogen (Caraway, 1955), total and free hydroxyproline (Goverde and Veenkamp, 1972) and alkaline ribonuclease (Scott *et al*, 1978).

Analysis of results

Differences between normal Asian and European pregnancies were tested for statistical significances using Student's 't' test. Differences

TABLE I

Description of mothers and babies in the study

	European			Asian		
Mothers	Normal	Hypertension but birth weight above 10th centile*	Birth weight below 10th centile	Normal	Hypertension but birth weight above 10th centile*	Birth weight below 10th centile
Number, Muslim (M) and Hindu (H)	32	18	8	13 M 11 H 2	4 M 3 H 1	4 M 4 H 0
Less than 155 cm	10	5	3	10	3	4
Age (years) Mean ± SD	25·8±6·69	28·7±7·6	28·5±5·0	27·0±1·68	27·25±8·38†	23·0±5·0
Primiparae	7	7	3	1	2	3
More than three previous pregnancies	8	3	2	4	1	1
Gestation (weeks) Mean ± SD	39·8±1·15	39·1±1·23	39·1±1·35	39·6±1·24	38·5±1·29	38·5±1·29
Placental weight (g) Mean ± SD	659±122	665±138	488±112	643±123	706±294	405±28·4
Baby measurements Mean ± SD						
Weight (Kg)	3·4±0·43	3·5±0·52	2·5±0·52	3·2±0·45	3·4±0·51	2·1±0·36
Centile score*	48·3±25·7	55·6±26·2	5·3±2·5	35·4±23·3	58·3±25·6	3·2±2·6
Length (cm)	50·7±2·1	50·9±1·7	47·4±2·0	50·3±1·46	51·3±3·57	46·5±2·02
Head circumference (cm)	35·0±1·3	35·2±1·53	32·6±1·76	34·5±1·01	35·2±1·67	32·4±1·3
Skinfold thickness (mm)	4·7±0·80	4·4±0·76	3·3±0·67	4·3±1·06	4·3±0·36	2·9±0·7
Mid-upper arm circumference (cm)	10·2±0·83	10·4±0·81	9·0±1·39	10·0±0·89	10·1±0·65	8·5±0·5

* Thomson *et al* (1968).

† Data on only three of four patients available.

between amniotic fluid from mothers with light-for-dates babies and well grown babies were tested using Chi squared analysis in an attempt to define a clinically useful cut-off point between pregnancies with well grown and light-for-dates babies.

RESULTS

Normal pregnancy

Table II shows the results from the 45 normal Asian and European pregnancies and they are compared with results obtained in our laboratory from the urine of newborn babies and pregnant mothers. There were no racial differences and amniotic fluids with higher ribonuclease levels tended to have higher α-amino nitrogen levels and in the Europeans lower urea nitrogen:total nitrogen ratios. Compared to newborn and maternal urine, the amniotic fluid contained proportionally less urea nitrogen and more uric acid and α-amino nitrogen when expressed as a percentage of the total nitrogen measured (namely urea, uric acid, creatinine and α-amino nitrogen). One-quarter of the total hydroxyproline was in the free form; this is a higher proportion than in maternal urine but lower than in neonatal urine.

Pregnancies with fetal growth failure

Amniotic fluid creatinine, α-amino, and urea nitrogen values in the abnormal pregnancies were similar to those in normal pregnancy.

Figure 1 shows the concentration of alkaline ribonuclease, total hydroxyproline and uric acid nitrogen in the abnormal pregnancies. Compared to results in normal pregnancies, the Asian mothers with light-for-dates babies had higher amniotic fluid ribonuclease levels and the European mothers with light-for-dates babies had lower amniotic fluid total hydroxyproline levels. When both races were considered to-

TABLE II

Biochemical values found in amniotic fluid and urine of normal mothers and in the urine of three-day-old low birth weight babies

Biochemical values	Amniotic fluid		Neonatal urine (n = 17)	Maternal urine at term	
	European (n = 32)	Asian (n = 13)		European (n = 25)	Asian (n = 11)
Urea N (mmol/l) Mean ± SD	11·4±3·2	10·2±3·0			
Per cent of total N*	65·5[b,c]	64·3	80·3	87·0	81·0
Uric acid N (mmol/l) Mean ± SD	1·47±0·39	1·50±0·28			
Per cent of total N*	8·4	9·4	6·6	3·4	4·0
Creatinine N (mmol/l) Mean ± SD	0·59±0·18	0·52±0·09			
Per cent of total N*	3·4	3·3	5·3	4·2	6·6
α-amino N (mmol/l) Mean ± SD	3·93±0·82[a,c]	3·65±0·62[a]			
Per cent of total N*	22·6	23·0	7·8	4·2	7·5
Free hydroxyproline (μmol/l) Mean ± SD	24·6±10·2	19·6±8·0			
Per cent of total hydroxyproline	31·9	25·2	41·7	22·1	19·3
Peptide hydroxyproline (μmol/l) Mean ± SD	52·4±17·5	58·2±21·0			
Per cent of total hydroxyproline	68·1	74·8	58·3	77·9	80·7
Alkaline RNase (units/l) Mean ± SD	685±122[a,b]	713±111[a]			

* expressed as % of sum of urea, uric acid, creatinine and α-amino N.

a. Alkaline RNase correlated with α-amino N: Europeans $r = 0·48$ $p < 0·001$; Asians $r = 0·55$ $p < 0·01$

b. Alkaline RNase correlated inversely with urea N: total N ratio in Europeans only: $r = -0·28$ $p < 0·05$

c. α Amino N correlated inversely with urea N: total N ratio in Europeans only: $r = -0·36$ $p < 0·01$

gether the mothers with light-for-dates babies had higher amniotic fluid uric acid nitrogen levels. Many of the individual results from mothers with light-for-dates babies were, however, well within the normal range and showed even more overlap with the results from those pregnancies complicated by hypertension but not failure of fetal growth.

Figure 2 shows the correlation between various constituents in amniotic fluids from both normal and abnormal pregnancies. In both races there was a significant positive correlation between ribonuclease and α-amino nitrogen, but while the Asian mothers with light-for-dates babies had both higher amniotic fluid ribonuclease and α-amino nitrogen levels, the results in the European mothers with light-for-dates babies were scattered along the regression line. Similarly, in the Europeans, while there was a negative correlation between amniotic fluid ribonuclease and urea nitrogen:total nitrogen ratio, the individual results in the pregnancies with light-for-dates babies were also scattered along the regression line. There was no significant correlation between amniotic fluid ribonuclease and the urea nitrogen:total nitrogen ratio in Asian mothers.

DISCUSSION

Physiology

The normal pregnancies gave similar results in both races. The nitrogen partition results deviated from those found in the urine of adults to an even greater extent than is found in the urine of the newborn. The low proportion of urea nitrogen found in the newborn was considered by Barlow and McCance (1947) to reflect starvation. The same argument might apply here but there is of course no way of establishing the fetal diet directly. The very high proportion of α-amino nitrogen presumably reflects both the greater plasma concentrations of amino acids in the fetus compared to the mother (Young and Prenton, 1969; Cockburn *et al*, 1973) and the reduced rate of amino acid reabsorption by the renal tubule (Sereni *et al*, 1955).

The relatively high proportion of nitrogen present as uric acid nitrogen in amniotic fluid and neonatal urine is unexplained. The newborn also excretes a relatively high proportion of nitrogen as uric acid but the amount excreted/kg body weight is low (Barlow and McCance 1947). It may be, therefore, that the high proportion of nitrogen present as uric acid is merely a mathematical consequence of the low proportion of urea nitrogen.

The total hydroxyproline concentration in the amniotic fluid was similar to that quoted by Kivirriko *et al*, (1963) and Shah *et al* (1972), and was substantially higher than that found by Wharton *et al* (1971). The proportions of free and peptide hydroxyproline were very similar to those found by Kivirriko *et al* (1963) and show a higher free hydroxyproline component than occurs in adults. It is not as high as that found in the newborn. Thus, though the increase in free hydroxyproline may be due to low fetal liver hydroxyproline oxidase activity (Morrow *et al*, 1967), it is probable that some free hydroxyproline crosses the placenta to be catabolised or excreted by the mother. Indeed the urinary excretion of free hydroxyproline is proportionally higher during pregnancy than in non-pregnant women (Dubovsky *et al*, 1968). Collagen turnover and growth rate are related to peptide hydroxyproline excretion in later life

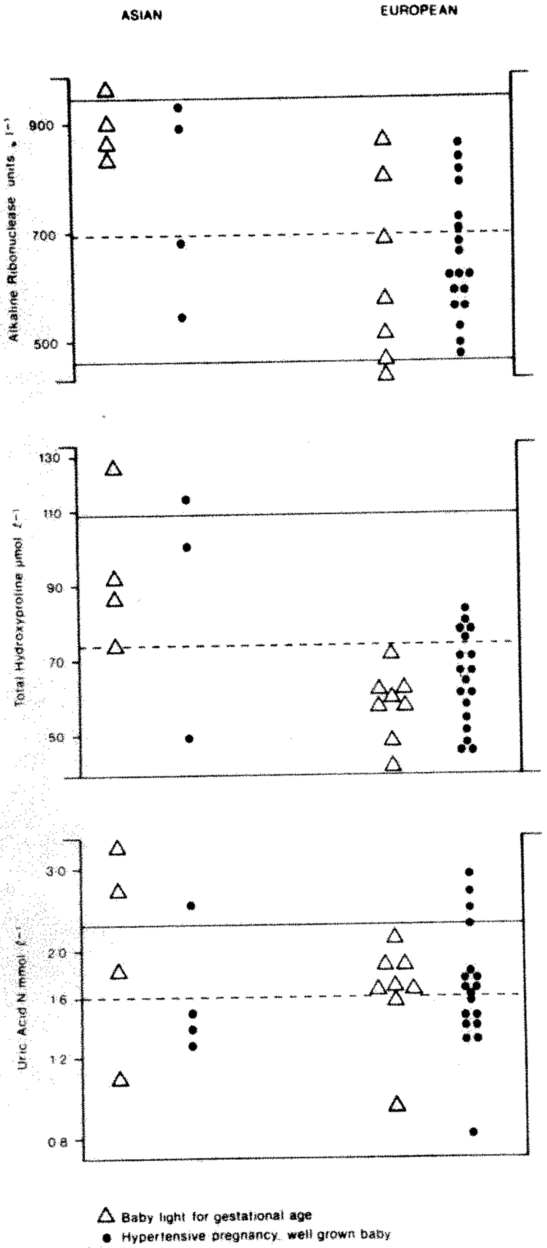

FIG. 1

FIG. 1—Left

Concentration of alkaline ribonuclease, total hydroxyproline and uric acid in amniotic fluid from normal and abnormal pregnancies. The boxed areas show the range (mean $\pm$ 2SD) observed in normal pregnancies (combined Asian and European results from Table II).
a) Ribonuclease in all 4 Asian mothers with light-for-dates babies was greater than 845 units/l whereas it was above that in only 4 of the 17 Asian mothers with well grown babies (Fisher exact probability $p = 0{\cdot}04$).
b) Total hydroxyproline in all 8 European mothers with light-for-dates babies was below 76 µmol/l whereas it was below that in only 28 of the 50 normal European mothers with well grown babies ($\chi^2 = 3{\cdot}95$; $p < 0{\cdot}05$).
c) When both races were considered together, uric acid was above 1·4 mmol/l in 10 out of the 12 mothers with light-for-dates babies whereas it was above that in only 31 of the 67 mothers with well grown babies ($\chi^2 = 4{\cdot}21$; $p < 0{\cdot}05$).

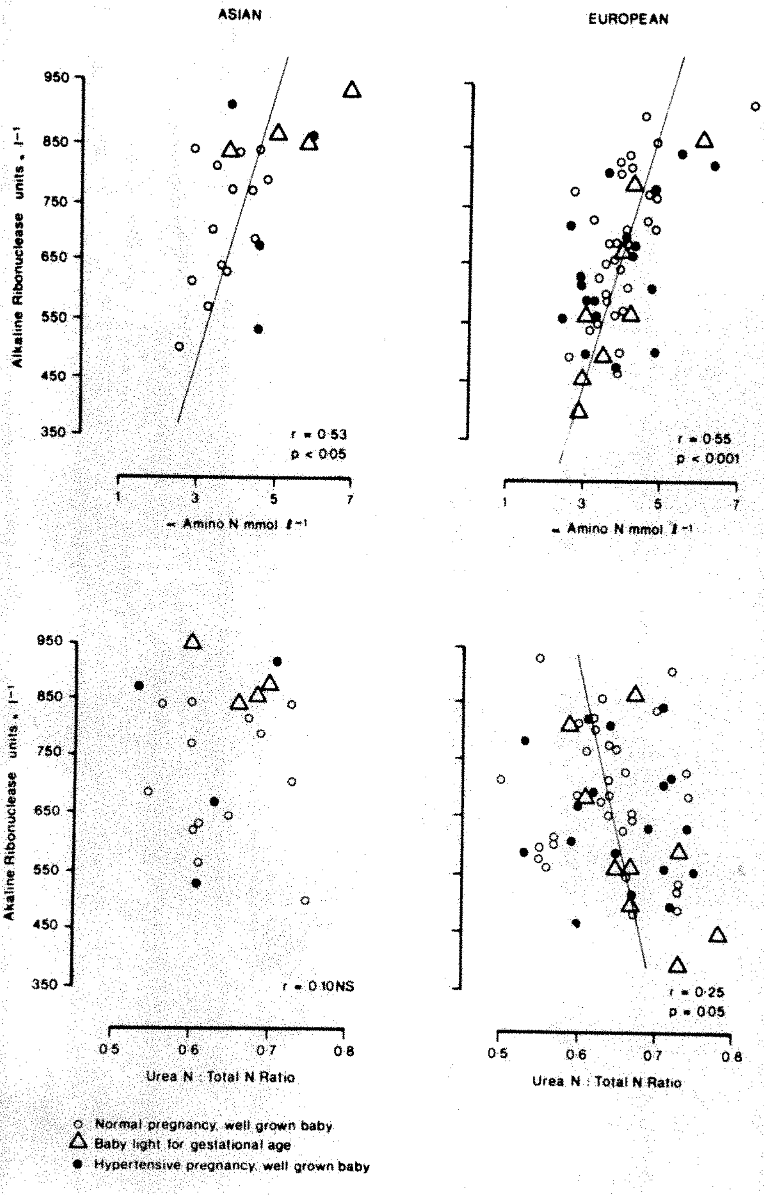

FIG. 2

Correlation of amniotic fluid alkaline ribonuclease with α-amino nitrogen and urea nitrogen-total nitrogen ratio in the three groups of pregnancies

but since at that time the free hydroxyproline excretion is low it often suffices to use total hydroxyproline without fractionation of its components. The large amounts of free hydroxyproline excreted by the fetus and newborn, however, may make total hydroxyproline excretion at this age less valid a measure of collagen turnover than it is later in life.

Pathogenesis of fetal growth failure

In European mothers, amniotic fluid which had a high ribonuclease and α-amino acid nitrogen had a lower urea nitrogen:total nitrogen ratio. These biochemical signs are found in the urine of malnourished toddlers who are not growing but, as Figure 2 shows, most of the European light for gestational age babies did not have such a combination.

In Asian mothers also, amniotic fluid ribonuclease correlated significantly with α-amino nitrogen and all four Asian mothers with light-for-dates babies showed high concentrations of both substances (Fig. 2). The Asian light-for-dates babies were therefore, unlike the European babies, showing some of the metabolic derangements seen in malnourished toddlers. The amniotic fluid from European mothers with light-for-dates babies had a lower total hydroxyproline level presumably reflecting the reduced fetal growth rate, but the amniotic fluid from similar Asian mothers did not show this. In a similar way many malnourished toddlers, despite their reduced growth rate, do not show a reduced total hydroxyproline excretion, probably because collagen breakdown is occurring. This could be regarded as supporting evidence that the fetal growth failure in the Asian mothers with light-for-date babies was due to chronic undernutrition of the fetus. For this argument to be convincing, however, we would have expected the four Asian mothers with light-for-dates babies to have had a low amniotic fluid urea nitrogen:total nitrogen ratio; as Figure 2 shows, they did not.

In both races, the amniotic fluid in mothers with light-for-dates babies had higher concentrations of uric acid nitrogen. We are unsure of the explanation. The observation achieved statistical significance only when both races were considered together, so that the European pregnancies were contributing most of the observed differences (but not reaching statistical significance when considered alone). The plasma uric acid concentration in mothers with hypertension is raised (McFarlane, 1963; Harrison, 1972) and since almost all the European mothers with light-for-dates babies were complicated by hypertension we wonder if this is the cause.

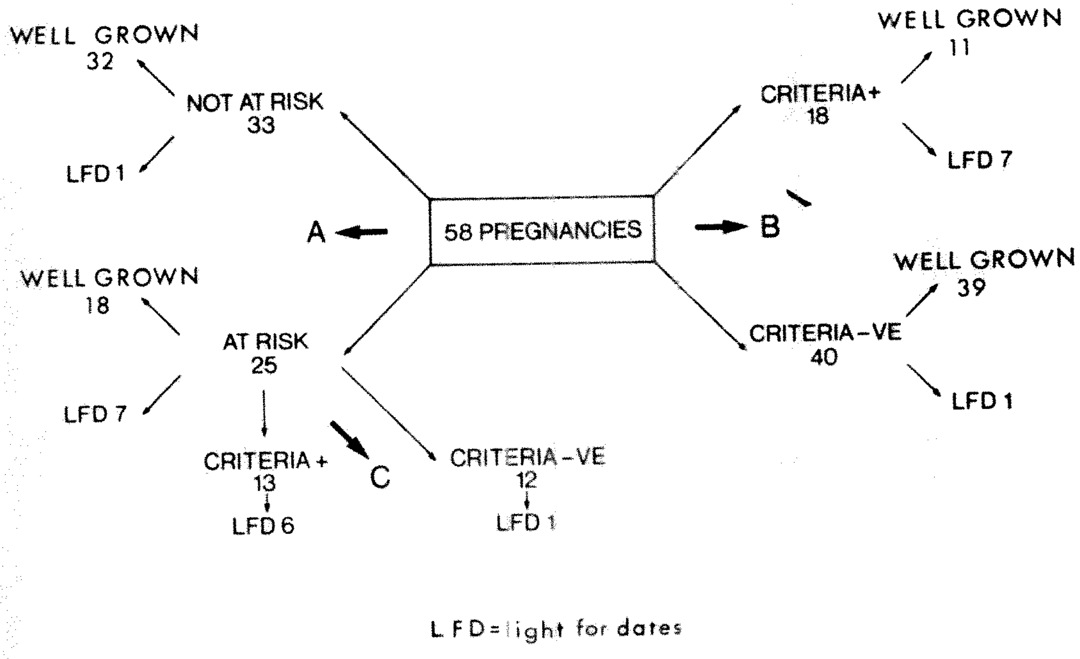

Fig. 3

Prediction of birth weight in European mothers using clinical criteria (A), biochemical criteria (B) or biochemical criteria in patients judged clinically to be at risk (C). Adverse biochemical results (i.e. criteria +): amniotic fluid uric acid greater than 1·5 mmol/l and total hydroxyproline less than 76 µmol/l. Adverse clinical features (i.e. criteria +): diastolic blood pressure greater than 90 mm Hg.

Whatever the exact reasons, the results in the Asian mothers with light-for-dates babies were different from the Europeans. This may indicate a different pathogenesis for the intrauterine growth failure.

Clinical implications

Although amniotic fluid total hydroxyproline, uric acid, and ribonuclease were significantly different in the mothers with light-for-dates babies, the overlap was so great as to limit clinical usefulness of the tests. A reduction in amniotic fluid total hydroxyproline has been shown before in European pregnancies with fetal growth retardation (Wharton *et al*, 1971). We hoped that fractionation of total hydroxyproline into its free and peptide components, would increase the discrimination of the test but it did not do so. Because no one test was convincing in isolation, a combination of total hydroxyproline and uric acid nitrogen was explored in Europeans in a simulated clinical situation (Fig. 3). Using biochemical criteria alone prediction ($\chi^2 = 10{\cdot}9$, $p < 0{\cdot}001$) was greater than using clinical criteria ($\chi^2 = 5{\cdot}5$, $p < 0{\cdot}025$). When biochemical criteria were applied to those clinically at risk, the prediction was further improved although this improvement did not reach statistical significance. Similarly a combination of tests, (alkaline ribonuclease more than 750 units/l; α-amino nitrogen more than 3·5 mmol/l) was examined in the Asian patients. This combination predicted light-for-dates babies more efficiently than clinical criteria alone, but was only marginally better than with alkaline ribonuclease alone. Clearly, none of these investigations can be used alone in the management of the individual pregnancy.

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OUTCOME OF PREGNANCY IN WOMEN USING DIFFERENT METHODS OF CONTRACEPTION

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Summary

During the years 1968–74, 17 032 women were recruited to the Oxford Family Planning Association prospective study of the effects of different methods of contraception. The present analysis, which concerns 5700 pregnancies experienced by the participants in the investigation, adds to the evidence that ex-users of oral contraceptives and intrauterine devices suffer no deleterious effects on the outcome of pregnancy in terms of miscarriage, ectopic gestation, stillbirth, congenital malformation, alteration in the sex ratio or reduction in birth weight. Accidental pregnancies in women taking oral contraceptives were few in the present study (66 in all), but it seems likely that harmful effects of exposure of the fetus to the pill *in utero*, if any, occur infrequently. Women experiencing an accidental pregnancy with an intrauterine device *in situ* are at a markedly increased risk of miscarriage and ectopic gestation and are more likely to give birth to an underweight infant than other women.

IN 1976, we described the outcome of the first 3051 pregnancies experienced by the participants in the Oxford Family Planning Association prospective study of the effects of different methods of contraception (Vessey *et al*, 1976). We present here a more comprehensive analysis relating to almost twice as many pregnancies and include, for the first time, a detailed consideration of congenital malformations.

METHODS

A full account of the methods used in the Oxford Family Planning Association study has been given elsewhere (Vessey *et al*, 1976). In brief, 17 032 women were recruited at one or other of 17 large family planning clinics in different parts of England and Scotland during the years 1968–74. At the time of recruitment each of these women had to be (a) aged 25 to 39 years; (b) married; (c) a white British subject; (d) willing to participate; and (e) either a current user of oral contraceptives of at least 5 months standing or a current user of a diaphragm or an intrauterine contraceptive device (IUCD) of at least 5 months standing without prior exposure to 'the pill'. During follow-up, each subject was questioned at return visits to the clinic by a doctor or a nurse and certain items of information were noted on a special form, including details of pregnancies and their outcome and changes in contraceptive practices together with the reasons for the changes. The date of the last menstrual period before conception was *not* routinely recorded. Women who defaulted were sent a postal version of the follow-up form and, if this was not returned, they were interviewed on the telephone or at a home visit. Copies of stillbirth certificates were obtained for babies born dead and reported malformations in liveborn infants were confirmed by correspondence with general practitioners or consultants. The work in each clinic was co-ordinated by a part-time research assistant and follow-up was maintained with an annual lapse rate for 'relevant' reasons (withdrawal of co-operation or loss of contact) of only about 0·3 per cent.

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The present analysis has been confined to pregnancies followed long enough for any type of outcome to be identified. The data for *planned* pregnancies are given both according to the method of contraception stopped to enable conception to occur and according to whether oral contraceptives had ever or never been used. The data for *unplanned* pregnancies are given only according to the method of contraception which failed.

RESULTS

Multiple pregnancy

Of the 4565 pregnancies lasting longer than 28 weeks, 60 (1·31 per cent) were multiple including one set of quintuplets. Table I shows the frequency of multiple pregnancy in relation to method of contraception, parity, and whether or not the pregnancy was planned. Planned pregnancies were less often multiple in women who had ever used the pill in comparison with those who had never done so (30 of 2927 *v* 19 of 1085; $\chi^2_{(1)} = 2\cdot88$; $P \simeq 0\cdot09$) while unplanned pregnancies in parous pill users were multiple more often than unplanned pregnancies in parous women using other methods of contraception (3 of 39 *v* 8 of 443; $\chi^2_{(1)} = 3\cdot24$; $P \simeq 0\cdot07$). Neither of these differences, however, reached conventional levels of statistical significance. Of the three sets of unplanned twins born to women using the pill, two were of like sex (both male/male) and one of unlike sex. The male infant in the latter set was stillborn and grossly malformed with an oval trunk and few recognisable internal organs.

Livebirths, stillbirths, miscarriages and ectopic gestations

Planned pregnancies. The study data for singleton planned pregnancies in nulliparous women are shown in Table II and for parous women in Table III. The Tables also provide some simple information about the age, social class and smoking habits of the women experiencing the pregnancies; women using the pill tended to be a little younger and slightly heavier smokers than those using the other methods of birth control. Of the 968 nulliparous and 1521

TABLE I

Multiple pregnancy in relation to method of contraception: data are rates per 100 pregnancies lasting longer than 28 weeks. Numerators and denominators are shown in parentheses

	Method of contraception*		
	Oral	IUCD	Other
Planned pregnancies†			
Nulliparous women	0·44 (4/906)	— (0/5)	1·29 (11/851)
Parous women	1·46 (13/892)	3·00 (6/200)	1·30 (15/1158)
Unplanned pregnancies‡			
Parous women	7·69 (3/39)	2·94 (2/68)	1·60 (6/375)

* Method stopped in order to conceive for planned pregnancies. Method which failed for unplanned pregnancies.

† When classified according to whether or not oral contraceptives had ever been used prior to conception the following figures were obtained:— Nulliparous used 0·69 (10/1456); not used 1·63 (5/306). Parous used 1·36 (20/1471); not used 1·80 (14/779).

‡ There were only 71 unplanned pregnancies lasting longer than 28 weeks in nulliparous women. None was multiple.

TABLE II

Outcome of singleton planned pregnancies in nulliparous women according to:— (i) the method of contraception stopped in order to conceive and (ii) whether or not oral contraceptives had ever been used prior to conception. Some characteristics of the women experiencing the pregnancies are also shown

	Method of contraception stopped						Use of oral contraceptives ever prior to contraception			
	Oral		IUCD		Other		Yes		No	
	No.	per cent	No.	per cent	No.	per cent	No.	per cent	No.	per cent
Outcome										
Livebirth—normal	856	84·1	5	—	801	83·4	1368	83·4	294	85·2
Livebirth—malformed	40	3·9	0	—	33	3·4	70	4·3	3	0·9
Stillbirth	6	0·6	0	—	6	0·6	8	0·5	4	1·2
Miscarriage	116	11·4	1	—	121	12·6	194	11·8	44	12·7
Subtotal	1018	100·0	6	—	961	100·0	1640	100·0	345	100·0
Ectopic gestation	3	0·3	0	—	0	0·0	3	0·2	0	0·0
Termination	5	0·5	0	—	1	0·1	6	0·4	0	0·0
Total	1026	—	6	—	962	—	1649	—	345	—
Per cent of women										
Aged 30 years or more	25·5		—		38·2		30·0		40·3	
From social classes IV or V	4·3		—		3·4		4·1		2·6	
Smoking 15 or more cigarettes/day	12·9		—		7·1		11·5		3·5	

parous women who discontinued some method of contraception other than the pill in order to conceive, only 345 (36 per cent) and 864 (57 per cent) respectively had never used oral contraceptives at *any* time. Although there are a number of minor differences between the contraceptive groups in Tables II and III, the only one worthy of note is the remarkably *low* rate of malformation among live infants born to nulliparous women who had never used the pill (3 of 297 *v* 70 of 1438; $\chi^2_{(1)} = 8{\cdot}74$; $P \simeq 0{\cdot}003$). While it seems unreasonable to ascribe this finding to chance, we have been unable to discover any other explanation; certainly the data for parous women do not show the same phenomenon.

Unplanned pregnancies. In total, 113 unplanned singleton pregnancies occurred in nulliparous participants in the study. Of these, six involved pill users (two resulting in a normal livebirth and four in a termination), one an IUCD user (resulting in a termination), and 106 users of other methods (resulting in 64 normal livebirths, four malformed livebirths, one stillbirth, 19 miscarriages and 18 terminations). The outcome of singleton unplanned pregnancies in parous women is shown in Table IV. The most striking feature is the remarkably unfavourable outcome in women using an IUCD, both in terms of miscarriage (111 of 177 *v* 95 of 500; $\chi^2_{(1)} = 115{\cdot}93$; $P < <0{\cdot}001$) and ectopic gestation (20 of 289 *v* 4 of 720; $\chi^2_{(1)} = 33{\cdot}39$; $P < <0{\cdot}001$). A detailed analysis of these data has been presented elsewhere (Vessey and Johnson, 1978). It was shown that there was little suggestion of any variation in outcome of pregnancy with type of device (Lippes Loop, Saf-T-Coil, Copper-7) but that pregnancies occurring accidentally after four or more years of IUCD use were particularly likely to be ectopic or to end in miscarriage. Nothing of value could be deduced about any effect of the position of the IUCD, since the great majority of devices were *in situ* both at conception and at delivery.

Congenital malformations

Data on selected congenital malformations among singleton planned infants born to

TABLE III

Outcome of singleton planned pregnancies in parous women according to:— (i) the method of contraception stopped in order to conceive and (ii) whether or not oral contraceptives had ever been used prior to conception. Some characteristics of the women experiencing the pregnancies are also shown

	Method of contraception stopped						Use of oral contraceptives ever prior to conception			
	Oral		IUCD		Other		Yes		No	
	No.	per cent	No.	per cent	No.	per cent	No.	per cent	No.	per cent
Outcome										
Livebirth—normal	843	84·4	190	87·1	1080	83·6	1383	84·1	730	84·5
Livebirth—malformed	28	2·8	3	1·4	47	3·6	50	3·0	28	3·2
Stillbirth	8	0·8	1	0·5	16	1·2	18	1·1	7	0·8
Miscarriage	120	12·0	24	11·0	150	11·6	195	11·8	99	11·5
Subtotal	999	100·0	218	100·0	1293	100·0	1646	100·0	864	100·0
Ectopic gestation	2	0·2	0	—	3	0·2	4	0·2	1	0·1
Termination	2	0·2	2	0·9	5	0·4	4	0·2	5	0·6
Total	1003	—	220	—	1301	—	1654	—	870	—
Per cent of women										
Aged 35 years or more	7·1		8·2		10·9		7·6		12·1	
From social classes IV or V	8·2		14·6		6·1		7·9		7·2	
Smoking 15 or more cigarettes/day	15·1		11·4		8·8		14·2		6·3	

TABLE IV

Outcome of singleton unplanned pregnancies in parous women according to the method of contraception which failed. Some characteristics of the women experiencing the pregnancies are also shown

	Method of contraception which failed					
	Oral		IUCD		Other	
	No.	per cent	No.	per cent	No.	per cent
Outcome						
Livebirth—normal	35	81·4	61	34·5	352	77·0
Livebirth—malformed	1	2·3	3	1·7	12	2·6
Stillbirth	0	0·0	2	1·1	5	1·1
Miscarriage	7	16·3	111	62·7	88	19·3
Subtotal	43	100·0	177	100·0	457	100·0
Ectopic gestation	0	0·0	20	6·9	4	0·6
Termination	14	24·6	92	31·8	202	30·5
Total	57	—	289	—	663	—
Per cent of women						
Aged 35 years or more	21·1		27·0		33·0	
From social classes IV or V	12·3		15·2		9·8	
Smoking 15 or more cigarettes/day	15·8		10·4		14·5	

TABLE V

Selected congenital malformations among singleton planned infants according to (i) the method of contraception stopped in order to conceive and (ii) whether or not oral contraceptives had ever been used prior to conception

		Method of contraception stopped						Use of oral contraceptives ever prior to conception			
		Oral		IUCD		Other		Yes		No	
ICD code	Type of malformation	No.	Rate/ 1000	No.	Rate/ 1000	No.	Rate/ 1000	No.	Rate/ 1000	No.	Rate/ 1000
227, 757·1	Haemangioma, lymphangioma, naevus	7	3·93			7	3·53	13	4·49	1	0·94
550–553	Hernia	5	2·81	1		6	3·03	8	2·76	4	3·75
740	Anencephalus	6	3·37			2	1·01	8	2·76	0	0·00
741	Spina bifida	3	1·68			3	1·51	5	1·73	1	0·94
742	Hydrocephalus	0	0·00			2	1·01	1	0·35	1	0·94
744	Anomalies of eye	0	0·00			4	2·02	3	1·04	1	0·94
746	Anomalies of heart	3	1·68			6	3·03	4	1·38	5	4·69
—	'Heart murmur'	8	4·49			4	2·02	10	3·45	2	1·88
749	Cleft palate and cleft lip	1	0·56			4	2·02	3	1·04	2	1·88
750·1	Pyloric stenosis	3	1·68			6	3·03	8	2·76	1	0·94
750·2	Tracheo-oesophageal fistula, oesophageal atresia and stenosis	4	2·25			1	0·50	5	1·73	0	0·00
751·1	Atresia and stenosis of small intestine	0	0·00			2	1·01	2	0·69	0	0·00
751·2	Atresia and stenosis of rectum and anal canal	0	0·00			1	0·50	0	0·00	1	0·94
752·4	Congenital hydrocoele	4	2·25			4	2·02	6	2·07	2	1·88
Remainder 752	Other genital anomalies	2	1·12			3	1·51	5	1·73	0	0·00
753	Anomalies of urinary system	1	0·56			2	1·01	2	0·69	1	0·94
754	Clubfoot	1	0·56			1	0·50	2	0·69	0	0·00
755·0–1	Polydactyly, syndactyly	0	0·00			3	1·51	1	0·35	2	1·88
755·2–4	Reduction deformity of limb	1	0·56			1	0·50	2	0·69	0	0·00
755·6	Congenital dislocation hip	6	3·37	1		6	3·03	10	3·45	3	2·81
—	'Clicking hip'	9	5·05			13	6·56	20	6·90	2	1·88
756·1	Anomalies of spine	2	1·12			2	1·01	4	1·38	0	0·00
759·3	Down's syndrome	1	0·56			2	1·01	2	0·69	1	0·94
Total infants		1781		199		1983		2897		1066	

nulliparous or parous women are given in Table V. Although the numbers of infants with any given abnormality are small, the data have been presented in detail to facilitate comparison with other studies. More than one abnormality was reported in about 10 per cent of the malformed infants; this implies that some infants are enumerated more than once in Table V. It should also be noted that Table V incorporates the available information about stillborn babies (principally derived from stillbirth certificates) as well as data concerning liveborn children. Malformations have been coded according to the 8th Revision of the International Classification of Diseases with the addition of two extra categories—'heart murmur' and 'clicking hip'. It seems likely that the great majority of infants included in these two categories did not, in fact, have any significant abnormality.

While there is substantial variation in the rates shown in Table V, none of the differences between the contraceptive groups reaches conventional levels of statistical significance. In general, the overall rates for each malformation are comparable with those reported in other similar series (e.g. Royal College of General Practitioners, 1976), suggesting that there is no gross under-reporting.

Congenital abnormalities occurring in singleton unplanned infants are listed in Table VI. The one malformed infant born to a woman who became pregnant while taking oral contraceptives

TABLE VI

Congenital malformations among singleton unplanned infants according to the method of contraception which failed

ICD code	Type of malformation	Method of contraception which failed		
		Oral	IUCD	Other
227, 757·1	Haemangioma, lymphangioma, naevus			3
740	Anencephalus		1	3
741	Spina bifida			2
743·8	Multiple ganglioneuromas, neuroblastoma			1
744·3	Cataract		1	
745·0	Aural dysgenesis			1
746	Anomalies of heart	1		1
748·3	Laryngeal stenosis			1
748·6	Hypoplasia of lung		1	
749	Cleft palate and cleft lip			1
751·1	Jejunal atresia			1
754	Clubfoot			4
755·5	Shoulder anomaly			1
755·6	Congenital dislocation of hip		1	
	'Clicking hip'			1
758·3	Thymic hypoplasia			1

was reported to have suffered from a cardiac defect and to have died shortly after birth. Unfortunately, no further details are available.

Sex ratio

The individual sex ratios shown in Table VII vary considerably but follow no consistent pattern. The only statistically significant difference between the contraceptive groups relates to planned infants born to nulliparous women (427 male out of 869 *v* 439 male out of 806; $\chi^2_{(1)} = 4{\cdot}55$; $P \simeq 0{\cdot}03$). It may be noted that the corresponding difference was much more marked in our earlier analysis (Vessey *et al*, 1976) and it seems reasonable to attribute it to chance.

Birth weight

Mean birth weights are given in Table VIII while Table IX is concerned with low birth weight infants (i.e. those weighing less than 2500 g). Both Tables show the expected difference between infants born to nulliparous and parous women. In addition, unplanned infants born to women using an IUCD were lighter on average than unplanned infants born to women using any other method of birth control (3·27 kg *v* 3·45 kg; $t = 2{\cdot}33$; $P \simeq 0{\cdot}02$) and were

TABLE VII

Sex ratio of births in relation to method of contraception: data are percentages of singleton livebirths which were male. Total numbers of livebirths are shown in parentheses

	Method of contraception*		
	Oral	IUCD	Other
Planned pregnancies†			
Nulliparous women	49·1 (869)	— (5)	54·5 (806)
Parous women	55·2 (843)	47·0 (183)	50·9 (1064)
Unplanned pregnancies			
Nulliparous women	— (2)	— (0)	35·5 (62)
Parous women	51·5 (33)	47·5 (59)	53·7 (333)

* Method stopped in order to conceive for planned pregnancies. Method which failed for unplanned pregnancies.

† When classified according to whether or not oral contraceptives had ever been used prior to conception the following figures were obtained: Nulliparous used 51·4 (1402); not used 52·9 (278). Parous used 53·3 (1397); not used 50·2 (693).

Note. The numbers included in this and the two succeeding Tables are smaller than those in earlier Tables since no enquiry was made about the sex or birth weight of infants in the early days of the study.

TABLE VIII

Weight of singleton livebirths in relation to method of contraception

	Birth weight (kg) Mean ± SE		
	Method of contraception*		
	Oral	IUCD	Other
Planned pregnancies†			
Nulliparous women	$3·33 \pm 0·02$	—	$3·35 \pm 0·02$
Parous women	$3·47 \pm 0·02$	$3·47 \pm 0·04$	$3·47 \pm 0·01$
Unplanned pregnancies			
Nulliparous women	—	—	$3·21 \pm 0·06$
Parous women	$3·39 \pm 0·14$	$3·27 \pm 0·08$	$3·46 \pm 0·03$

* Method stopped in order to conceive for planned pregnancies. Method which failed for unplanned pregnancies.

† When classified according to whether or not oral contraceptives had ever been used prior to conception the following figures were obtained: Nulliparous used $3·33 \pm 0·01$; not used $3·40 \pm 0·03$. Parous used $3·47 \pm 0·01$; not used $3·48 \pm 0·02$.

TABLE IX

Low birth weight (less than 2500 g) in relation to method of contraception: data are rates per 100 singleton livebirths. Numbers of infants with low birth weight are shown in parentheses

	Method of contraception*		
	Oral	IUCD	Other
Planned pregnancies†			
Nulliparous women	4·25 (37)	—	3·60 (29)
Parous women	2·02 (17)	2·19 (4)	1·60 (17)
Unplanned pregnancies			
Nulliparous women	—	—	6·45 (4)
Parous women	9·09 (3)	13·56 (8)	2·40 (8)

* Method stopped in order to conceive for planned pregnancies. Method which failed for unplanned pregnancies.

† When classified according to whether or not oral contraceptives had ever been used prior to conception, the following figures were obtained: Nulliparous used 4·28 (60); not used 2·52 (7). Parous used 2·08 (29); not used 1·30 (9).

more often of low birth weight (8 of 59 *v* 11 of 366; $\chi^2_{(1)} = 10·90$; $P \simeq 0·001$).

Other analyses

Harlap and Davies (1978), on the basis of a study of 16 826 babies born in Jerusalem in the years 1974–76, have suggested that an adverse pregnancy outcome may occur after oral contraceptive use in women over the age of 35 and in those who are underweight for their height. Accordingly, we undertook special analyses to try to detect any such interactions; none was found. The relatively small size of our sample should, of course, be born in mind in interpreting this result.

DISCUSSION

Multiple pregnancy

Our data suggest that multiple pregnancy may occur a little less often in ex-users of oral contraceptives than in other women. A similar result has been reported in a number of other studies (Royal College of General Practitioners, 1976; Rothman, 1977; Harlap and Davies, 1978). Some authors, however, have suggested that twinning may actually be *increased* in certain subgroups of ex-users—for example in those conceiving within one month of cessation of oral contraceptive use (Rothman, 1977) and in those conceiving after discontinuation of sequential preparations or those containing high doses of oestrogen (Harlap and Davies, 1978). Our data are too few to confirm or refute these findings.

With regard to unplanned pregnancies occurring during oral contraceptive use, our finding of an excess of multiple births has also been reported by others (Hines and Goldzieher, 1968; Harlap and Davies, 1978). It should be noted, however, that there were no twins among the 102 births following pill failure in the Study by the Royal College of General Practitioners (1976).

Livebirths, stillbirths, miscarriages and ectopic gestations

In accord with our own findings, most authors are agreed that ex-users of the pill are not at an increased risk of stillbirth, miscarriage or ectopic gestation (Peterson, 1969; Royal

College of General Practitioners, 1976; Rothman, 1977; Harlap and Davies, 1978). Indeed, there is some evidence that these unfavourable outcomes of pregnancy may be less common in women discontinuing the pill than in other women.

Our data on unplanned pregnancies in pill users are few; like those reported by the Royal College of General Practitioners (1976), they suggest no adverse effects of oral contraceptives on the risk of stillbirth, miscarriage or ectopic gestation. The Jerusalem study included 108 infants conceived while their mothers were taking the pill (Harlap and Davies, 1978). Of these, three died in the perinatal period while only 1·5 such deaths would have been expected from the experience of the control series. This difference, however, was not statistically significant.

The unfavourable outcome of unplanned pregnancies occurring in women using an IUCD, both in terms of ectopic gestation and miscarriage, is well recognised and requires no further discussion here (for recent reviews see Tatum and Schmidt, 1977; Vessey and Johnson, 1978).

Congenital malformations

Prospective studies of possible teratogens (like oral contraceptives) must be very large (including, say, 50 000 births) before confident conclusions can be drawn about the absence of any adverse effects on individual malformations or particular combinations of malformations. None the less, our results concerning planned pregnancies in ex-users of the pill are reassuring; the one statistically significant difference which we did detect (Table II) certainly seems to be attributable to an unexpectedly *low* rate of malformation among live infants born to nulliparous women who had never used the pill. Reassuring conclusions about the risk of malformation in infants born to ex-users of the pill have also been reached in most other large prospective studies (Peterson, 1969; Royal College of General Practitioners, 1976; Rothman and Louik, 1978). Harlap and Davies (1978), however, while finding that infants born to former pill-users had lower *overall* rates of malformation than those born to other women, suggested that certain subgroups of ex-users (those of low relative weight, those over the age of 35 and those of Asian origin) were at an *increased* risk of having an abnormal child, especially one with Down's syndrome. Insofar as we have been able to search for such interactions in our data, the results have been negative. It should also be noted that Janerich *et al* (1976) have reported the results of a case-control study of 103 mothers of infants with Down's syndrome and an equal number of matched controls. There was no evidence of any increased pill use among the mothers of the abnormal infants either in the year before pregnancy or during pregnancy itself.

The literature relating to the risk of malformation in infants born to mothers experiencing an unplanned pregnancy while taking the pill is large, contradictory and confusing. Much of the difficulty arises from the fact that many authors have considered together in the same series women who have become accidentally pregnant while taking oral contraceptives, those using hormonal pregnancy tests and those receiving hormones for the treatment of threatened or habitual abortion. This practice seems to us to be quite incorrect. Among the malformations particularly under suspicion are defects of the heart and great vessels, multiple abnormalities described as the VACTERL syndrome, limb reduction deformities and neural tube defects (Janerich *et al*, 1974; Nora *et al*, 1978; Harlap and Davies, 1978). While the present study is too small for any firm conclusion to be drawn, our findings, taken in conjunction with those reported by the Royal College of General Practitioners (1976), leave little doubt that a woman experiencing an accidental pregnancy while taking the pill is unlikely to give birth to a malformed child.

There seems to be no evidence other than a handful of case reports that IUCD's are associated in any way with an increased risk of malformation (Guillebaud, 1976). Our data, though few, add reassurance on this point.

Sex ratio

Those authors who have reported on substantial series of births have uniformly come to the conclusion that oral contraceptive use has no detectable effect on the sex ratio (Rothman and Leiss, 1976; Royal College of General Practitioners, 1976; Harlap and Davies, 1976). Our findings are in accord with those of others.

Birth weight

The results of the present study suggest that oral contraceptive use has little, if any, effect on birth weight. Rothman (1977) came to a similar conclusion while Harlap and Davies (1978) reported that ex-pill users had significantly fewer low birth weight babies than other women.

Our finding of a significant excess of low birth weight infants born to women with an IUCD *in situ* was, perhaps, not unexpected in view of the high risk of miscarriage in these subjects. Similar results have been reported by Steven and Fraser (1974).

CONCLUSION

The present analysis adds to the evidence that ex-users of oral contraceptives and IUCD's suffer no deleterious effects on the outcome of pregnancy. Data concerning accidental pregnancies in women using the pill are few, but it seems likely that the harmful effects of exposure to oral contraceptives *in utero*, if any, occur infrequently. Women experiencing an accidental pregnancy with an IUCD *in situ* are at a markedly increased risk of ectopic gestation and miscarriage and are more likely to give birth to an underweight infant than other women.

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MULTIPLE BIRTHS IN FORMER ORAL CONTRACEPTIVE USERS

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Summary

Multiple births were studied in a cohort of 2953 former oral contraceptive users and 13 630 controls, all the women were interviewed post partum. There were 238 multiple births, a rate of 14·4/1000 deliveries. Former oral contraceptive users had 13·5/1000 sets of multiple births compared to 14·5/1000 in the controls. When women who had received treatment for anovulation were excluded, these rates were 11·1 and 12·7/1000 respectively, a difference which is not statistically significant. There was, however, a significant deficit of multiple births among the small group of former pill users who were underweight in relation to their height at the time of conception. Multiple births were also increased after stopping sequential pills and preparations containing high doses of oestrogen, and there was an excess of multiple births following breakthrough pregnancies. These findings, although statistically significant, are based on small numbers, and require confirmation from other studies.

BENIRSCHKE AND KIM (1963) have speculated that pituitary gonadotrophin secretion might be increased following cessation of oral contraceptive therapy, leading to the possibility of an increase in multizygotic multiple births. Clinical evidence to support or refute this hypothesis is scanty and difficult to interpret. There is no evidence that multiple births have become more frequent since the introduction of the pill. On the contrary, multizygous multiple pregnancy rates have been falling since 1960 in many industrial countries, and the change cannot be explained wholly by alterations in the distribution of maternal age or parity (Editorial, 1976). James (1972) has speculated that exogenous sex hormones such as stilboestrol or oral contraceptives, or environmental pollutants such as pesticides, may be responsible for a reduction in superovulation.

This paper describes multiple pregnancies observed in a retrospective cohort study of oral contraceptive users and controls, and presents evidence both for a small overall decrease in multiple birth rates in former users, and for an increase in multiple births following the use of sequential pills and following breakthrough pregnancies.

METHODS

All women who were delivered in the three largest of West Jerusalem's four obstetric hospitals during a two-year period were interviewed on the first postpartum day. Questions were asked about oral and other contraceptives used since any previous pregnancy, contraceptive failures, the time taken to conceive and other items. Information about multiple births and demographic data on the parents were ascertained independently. The study, which has been described in detail elsewhere (Harlap and Davies, 1978), covered over 98 per cent of the women who were delivered in the target hospitals and 93 per cent of Jewish births in the West Jerusalem area, and was conducted within the framework of the Jerusalem Perinatal Study (Davies *et al*, 1969; Harlap *et al*, 1977).

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RESULTS

There were 16 583 deliveries in the study, with 238 sets of multiple births, a rate of 14·4/1000. There were 75 unlike-sexed sets, giving according to the Weinberg (1909) formula a multizygous pregnancy rate of 9·1 and a monozygous rate of 5·3/1000. This estimate for the monozygous rate is considerably higher than the rates of around 3·5 reported from a large number of studies (Hytten and Leitch, 1971). Table I shows the estimates for monozygous and multizygous rates by maternal age. Unlike-sexed sets increased in frequency with maternal age, as has been reported previously. Monozygous sets varied little among the four age-groups of women aged under 35. Over 35, they increased slightly. This pattern is also consistent with previously-reported age differences in the incidence of monozygous multiple pregnancies (Hytten and Leitch, 1971). However, the overall rate of 5·3/1000 is so high, that we think it would be unwise to use the Weinberg formula to compare mono- and multizygous multiple pregnancy rates in relation to oral contraceptive use in our population.

The 2953 oral contraceptive users had slightly fewer sets of multiple births than controls (13·5 versus 14·5/1000). The difference was not statistically significant, nor was it consistent in subgroups of age, birth order, education, or social class. There were 39 sets of twins (13·2/1000) born to former pill users and one set of triplets (0·34/1000) compared to rates of 14·1 and 0·44 in nonusers.

Among the former oral contraceptive users there were 65 women who had treatment with clomiphene or human menopausal gonadotrophin (Pergonal) prior to conception. There were 12·3 per cent multiple births in these women compared to 7·9 per cent among the 365 control women who were treated for anovulation. The difference is not statistically significant.

Among women *not* treated for anovulation the rate of multiple births was 11·1 in the oral contraceptive group and 12·7 in the controls. Multiple regression analysis (results available from the author on request) showed an average deficit of 1·3/1000 multiple births in former pill users, after taking into account the effects of maternal age, education, and religious observance.

Table II shows rates of multiple births by age and interval since stopping oral contraceptive medication. There was no excess of multiple births in women conceiving soon after stopping the pill. However, there was a significant excess of multiple births among the 104 breakthrough pregnancies reported in this study, with four sets of twins occurring in them, a rate of 38·5/

TABLE I

Multiple births by maternal age, and estimated multizygous and monozygous sets, according to the Weinberg (1909) formula

	Age of Mother						Total (including unknown)
	Under 20	20–24	25–29	30–34	35–39	40+	
Deliveries	553	5134	5821	3127	1504	405	16 583
Sets of multiple births	5	56	95	42	37	3	238
rate/1000	9·0	10·9	16·3	13·4	24·6	7·4	14·4
Unlike-sexed sets	1	15	33	13	13	0	75
Estimated multizygous	2	30	66	26	26	0	150
rate/1000	3·6	5·8	11·3	8·3	17·3	0	9·1
Estimated monozygous	3	26	29	16	11	3	88
rate/1000	5·4	5·1	5·0	5·1	7·3	7·4	5·3

TABLE II

Multiple births by maternal age and interval between stopping oral contraceptive therapy and conception (excludes women treated for anovulation)

Months since stopping oral contraceptives	Age of Mother			Total (including unknown)
	Under 25	25–34	35+	
0–2				
Deliveries	419	862	71	1355
Multiple/1000	11·9	10·4	28·2	11·8
3+				
Deliveries	296	909	102	1309
Multiple/1000	3·4	12·1	39·2	12·2
Total pill users (including unknown intervals)				
Deliveries	766	1905	212	2888
Multiple/1000	7·8	10·5	28·3	11·1
Nonusers				
Deliveries	487	6768	1647	13 265
Multiple/1000	10·6	13·2	17·6	12·7

TABLE III

Multiple births by oral contraceptive use, height, and relative weight (excludes women treated for anovulation)

	Pill users		Nonusers		Total	
	Deliveries	Multiple sets/1000	Deliveries	Multiple sets/1000	Deliveries	Multiple sets/1000
Height (cm)						
Under 160	738	6·8*	3673	12·3	4411	11·3
160–164	908	13·2	4123	13·1	5031	13·1
165+	1155	10·4	4464	11·6	5619	11·4
Pre-pregnant weight centile (within height)						
Under 20	441	4·5†	1612	12·4	2053	10·7
20–49	774	10·3	2838	11·3	3612	11·1
50–79	914	13·1	3914	12·5	4828	12·6
80+	656	10·7	3705	13·2	4361	12·8
Total (including unknowns)	2888	11·1	13 265	12·7	16 153	12·4

*$p < 0{\cdot}05$, †$p < 0{\cdot}02$, compared with nonusers.

1000 compared with 10·0/1000 in other oral contraceptive users not treated for anovulation ($p < 0{\cdot}001$).

The deficit of multiple pregnancy in oral contraceptive users was statistically significant for short women and those who were slender, or low weight, relative to their height at the time of conception (Table III). These results should be interpreted with caution, because 'significant' findings may arise by chance in studies such as this one, in which a large number of subgroups of women have been examined. They are of greater interest, however, when viewed against other findings in the study. Anovulation was reported significantly more frequently in slender pill users compared to slender controls (Harlap and Davies, 1978). Obese pill users, on the other hand, reported no excess of anovulation. Coupled with the decreased multiple pregnancy rate observed here, this suggests that underweight pill users had a continued failure of gonadotrophin release after stopping medication, a failure not experienced by women of adequate weight.

Pill users aged over 35 had an increased frequency of multiple births compared to controls of the same age. Although the difference was not significant it was paralleled by excess risk of other undesirable reproductive outcomes in older oral contraceptive users whose offspring also had more major congenital malformations and perinatal mortality than those of controls

TABLE IV

Multiple births by pharmacologic composition of oral contraceptives (excludes women treated for anovulation)

Composition of oral contraceptives	Age of Mother			Total (including unknown)
	Under 25	25–34	35+	
Oestrogen dose				
Up to 0·05 mg				
Births	299	866	77	1244
Multiple/1000	6·7	6·9	13·0	7·2
Over 0·05 mg				*
Births	345	806	82	1234
Multiple/1000	11·6	16·1	36·6	16·2
Progestogen dose				
under 3 mg				
Births	406	1084	95	1587
Multiple/1000	2·5	11·1	10·5	8·8
3 mg or more				
Births	239	589	64	893
Multiple/1000	20·9	11·9	46·9	16·8
Progestogen type				
19–nor				
Births	606	1519	146	2274
Multiple/1000	9·9	11·2	27·4	11·9
17–α				
Births	39	155	13	207
Multiple/1000	0	12·9	0	9·7
Regime				
Combined				
Births	521	1438	137	2099
Multiple/1000	5·8	10·4	14·6	9·5
Sequential				*
Births	123	234	22	379
Multiple/1000	24·4	17·1	90·9	23·7
Total pill users (including other and unknown)				
Births	766	1905	212	2888
Multiple/1000	7·8	10·5	28·3	11·1
Nonusers				
Births	487	6768	1647	13 265
Multiple/1000	10·6	13·2	17·6	12·7

*p <0·05

aged 35 or more. In addition, older pill users took longer to conceive, and those who had used the pill before their previous pregnancy reported more miscarriages than older control women (Harlap and Davies, 1978).

Table IV shows rates of multiple births for women using different pharmacologic types of pills, by maternal age. There was a consistent and significant excess of multiple births associated with sequential preparations and those containing high doses of oestrogen.

DISCUSSION

This study is based on rather small numbers, and the findings need to be confirmed by others. The results are similar to those of several previous studies showing a small deficit in multiple pregnancy rates in oral contraceptive users (Royal College of General Practitioners, 1976; Vessey *et al*, 1976; Rothman, 1977). Two other authors (Konefka, 1974; Rice-Wray *et al*, 1971) also reported no excess of multiple pregnancies in women who conceived after taking the pill, while others who studied births in oral contraceptive users (Peterson, 1969; Robinson, 1971) made no mention of multiple births.

Vandenberg *et al* (1974) reported differing pituitary responses to luteinizing hormone releasing factor (LHRF) in women taking combined oral contraceptives, as opposed to sequentials. The LH response was increased, though delayed, after sequentials, but not after combined hormones. This suggests that multiple pregnancies might be increased in conceptions occurring in women while taking sequentials, or shortly after stopping them. Support for this hypothesis comes from the study by Hines and Goldzieher (1968) in which there was a large excess of multiple births in a group of sequential contraceptive failures. Our study also shows a significant excess of multiple births in women who have used sequential pills, but not in those who took combined ones.

The excess of multiple births in breakthrough pregnancies observed in this study is also in agreement with previous reports. In addition to the study of failures while using sequentials (Hines and Goldzieher, 1978), Vessey *et al* (1976) observed an excess of multiple births in a small group of breakthrough pregnancies in women taking both sequentials and combined preparations. On the other hand, there were no multiple pregnancies in the 102 births following pill failures in the study done by the Royal College of General Practitioners (1976). Janerich *et al* (1974) reported an excess of multiple births among babies with limb-reduction deformities who were conceived while their mothers were taking contraceptive pills, and suggested that both multiple and breakthrough pregnancies may occur in women with a hyperactive endocrine system.

Janerich (1974) drew attention to the importance of the time interval between stopping the pill and conception. Rothman (1977) observed a small excess of multiple pregnancies among women who conceived soon after stopping the pill. There are too few patients in this study to refute this observation, but the available evidence does not support it.

Our results suggest that there may be an interaction between maternal age and oral contraceptives for multiple births. The deficit in multiple births in former pill users was greatest for young women (Table II), but elderly pill users had a higher multiple pregnancy rate than controls aged 35 or more. While these differences may well have arisen by chance, a similar pattern was observed in the study by the Royal College of General Practitioners (1976). Furthermore, there is ample evidence for an interaction between age and oral contraceptive use for other side effects (Mann and Inman, 1975). It would be of interest to know if pituitary responses to LHRF differ in oral contraceptive users of different ages.

In summary, this study provides some evidence in support of the hypothesis advanced by Benirschke and Kim (1973) for an increase in pituitary gonadotrophin release in women recently stopping oral contraceptives. The results suggest that the increase may occur after stopping sequential pills, but not after combined ones and this could be explained by a differing pituitary response to LHRF in women stopping the two types of medication (Vandenberg *et al*, 1974). On the other hand, the decreased multiple pregnancy rate in underweight pill users, and the excess anovulation reported by these women (Harlap and Davies, 1978) points to the possibility of a *decrease* in gonadotrophic function in some slender women stopping oral contraceptive medication. Because only small numbers were available in this study, these findings require confirmation, preferably from studies in areas of the world where malnutrition is common, or where, like in Israel, self-medication of healthy women with vitamins is uncommon.

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EFFECT OF VARYING AMOUNTS OF ETHINYL OESTRADIOL IN THE COMBINED ORAL CONTRACEPTIVE ON PLASMA SEX HORMONE BINDING GLOBULIN CAPACITY IN NORMAL WOMEN

BY

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Summary

The plasma sex hormone binding globulin (SHBG) capacity has been measured in 52 normal women, 11 women on various oral contraceptives containing 50 μg of ethinyl oestradiol and 11 women on oral contraceptives containing less than 35 μg of ethinyl oestradiol. The results show that women on oral contraceptives containing 50 μg of ethinyl oestradiol have a significantly raised SHBG capacity ($p < 0 \cdot 005$) whereas those patients on oral contraceptives containing 35 μg or less of ethinyl oestradiol have SHBG capacities which do not differ significantly from normal ovulating women ($p > 0 \cdot 05$). Thus the 35 μg pill interferes less with bound/unbound sex steroid ratios than does the 50 μg pill.

At the introduction of oral contraceptive therapy, the combined pill contained relatively large doses of oestrogen. In the face of a clear causal relationship between cardiovascular disorders and the high dose oestrogen oral contraceptive (Vessey *et al*, 1977; Royal College of General Practitioners Study, 1977) it was felt desirable to reduce substantially the oestrogen content of the combined oral contraceptive pill. The advent of the potent progestogens allowed complete ovulatory suppression using very small doses of oestrogen.

Plasma sex hormone binding globulin (SHBG) capacity is altered by the sex steroids. It is substantially increased by the oestrogens (Murray *et al*, 1973) and somewhat reduced by progestogens (Anderson, 1974). Earlier studies have shown that the combined oral contraceptive agents increase SHBG capacity (Thijssen and van Kammen, 1975), and thus it would appear that even when progestogens are administered, SHBG capacity is a sensitive index of oestrogenization.

The object of this study was to measure the plasma SHBG capacity in two groups of women, one taking a combined pill containing 50 μg of ethinyl oestradiol and a second group taking a combined pill containing 35 μg or less of ethinyl oestradiol. The SHBG capacity in these two groups was then compared with that in 52 normal ovulating women.

PATIENTS AND METHODS

Twenty-two normal women on oral contraceptive therapy were studied. All had been taking oral contraceptive pills for more than six months. The hormone combinations being taken by these 22 women are shown in Table I.

A further group of 52 women at different stages of a normal ovulatory cycle was studied for comparison. None of these subjects had taken any form of hormonal contraceptive for

TABLE I

Number of patients and types of oral contraceptive used

Ethinyl oestradiol (µg)	Progestogen	Number of patients
50	1 mg Norethisterone acetate (Minovlar)	4
	3 mg Norethisterone acetate (Gynovlar)	1
	1 mg Ethinodioldiacetate (Ovulen 50)	2
	2·5 mg Norethisterone acetate (Norlestrin)	1
	4 mg Norethisterone acetate (Anovlar)	1
	0·5 mg Norgestrel (Ovran)	1
	2·5 mg Gynoestrenol (Minilyn)	1
35	0·5 mg Norethisterone (Ovysmen)	1
30	0·25 mg Norgestrel (Eugynon)	5
	0·15 mg Norgestrel (Microgynon, Ovranette)	4
20	1 mg Norethisterone acetate (Loestrin)	1

the previous six months. All were fertile and were using other methods of birth control.

Measurement of SHBG capacity

The method of assay used was that described by Rudd *et al* (1974), and was based on the degree of binding of isotopically labelled testosterone to SHBG.

An aliquot of 200 µl of plasma was mixed with 200 µl of 5 per cent Charcoal suspension ('Norit A', Sigma Chemical Company) in 0·1 M phosphate buffer at pH 7·4. The mixture was vortexed for 10 seconds and allowed to stand for 30 minutes. In this way, any endogenous steroids in the plasma sample were removed. The mixture was then centrifuged for 10 minutes at $2{\cdot}5 \times 10^3 g$ and 200 µl of the supernatant removed; to this aliquot of supernatant were added 50 µl of ($4^{14}C$) testosterone with a specific activity of 53·5 mC/mmol (Radiochemical Centre, Amersham). After mixing, the solution was allowed to stand for 2 hours at room temperature after which the SHBG, now binding the labelled testosterone, was precipitated by the addition of 250 µl of saturated ammonium sulphate. The mixture was then re-centrifuged and the supernatant decanted. The precipitate was redissolved in 200 µl of the phosphate buffer and 100 µl of this solution was removed and counted for 20 minutes, in 7 ml PCS ('Phase Combining System', Amersham/Searle Corporation, USA) in a Wallac beta counter.

Each specimen was assayed in duplicate. Two quality control sera were assayed in duplicate in each assay. The interassay coefficient of variation was 8·1 per cent for 28 assays.

Results are expressed as µg of bound testosterone/100 ml of plasma (µgT/100 ml). The mean ± 1 SEM of these values is quoted throughout and statistical comparisons were made between the groups using Student's 't' test.

RESULTS

The mean plasma SHBG capacity in the 52 normal ovulating women was $2{\cdot}31 \pm 0{\cdot}05$, the range of values lying between 1·53 to 2·98 (Figures 1 and 2).

The mean plasma SHBG capacity in the women on 50 µg oral contraceptives was $2{\cdot}73 \pm 0{\cdot}133$ and that of women on a pill containing 35 µg or less of ethinyl oestradiol was $2{\cdot}2 \pm 0{\cdot}115$. There was a significant elevation of SHBG capacity in women on the 50 µg ethinyl oestradiol oral contraceptive when compared with normal untreated women ($p < 0{\cdot}005$; Fig. 1). However, a similar comparison between the SHBG capacity in women on 35 µg or less or contraceptives showed no difference from those seen in normal women ($p > 0{\cdot}5$; Fig. 2).

DISCUSSION

All oestrogens, whether they be naturally occurring or synthetic steroids, elevate plasma SHBG capacity (Anderson, 1976). Progestogen however reduces SHBG capacity (Anderson, 1974). In this way, the ratio of bound to unbound steroids, and thus the biological availability, is controlled by the SHBG content of the blood. It has been shown that synthetic progestogens used in doses comparable with those present in the combined oral contraceptive on their own significantly reduce SHBG levels (Thijssen and van Kammen, 1975). However, this study shows

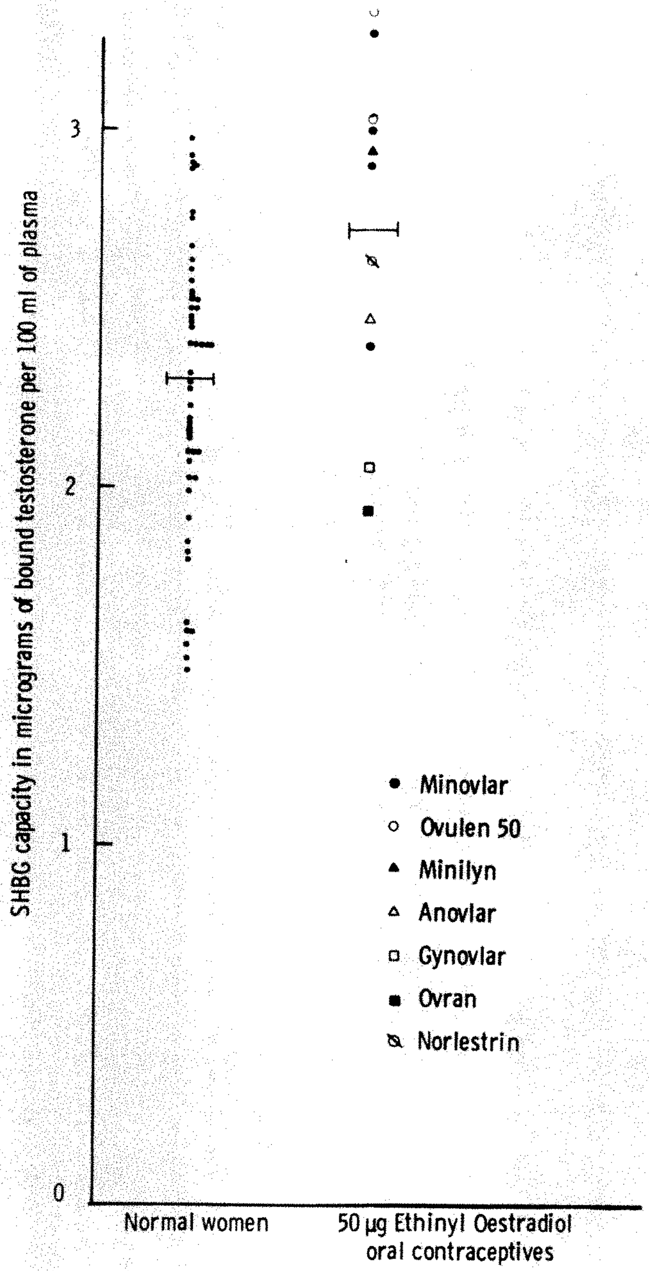

FIG. 1

On the left are depicted the individual values of plasma SHBG capacity in normal ovulating women and on the right the values seen in women taking a combined oral contraceptive containing 50 µg of ethinyl oestradiol. The mean values in the two groups are shown as horizontal bars. There is a significant increase in SHBG capacity in these pill patients over that in the untreated ovulating women ($p < 0{\cdot}005$).

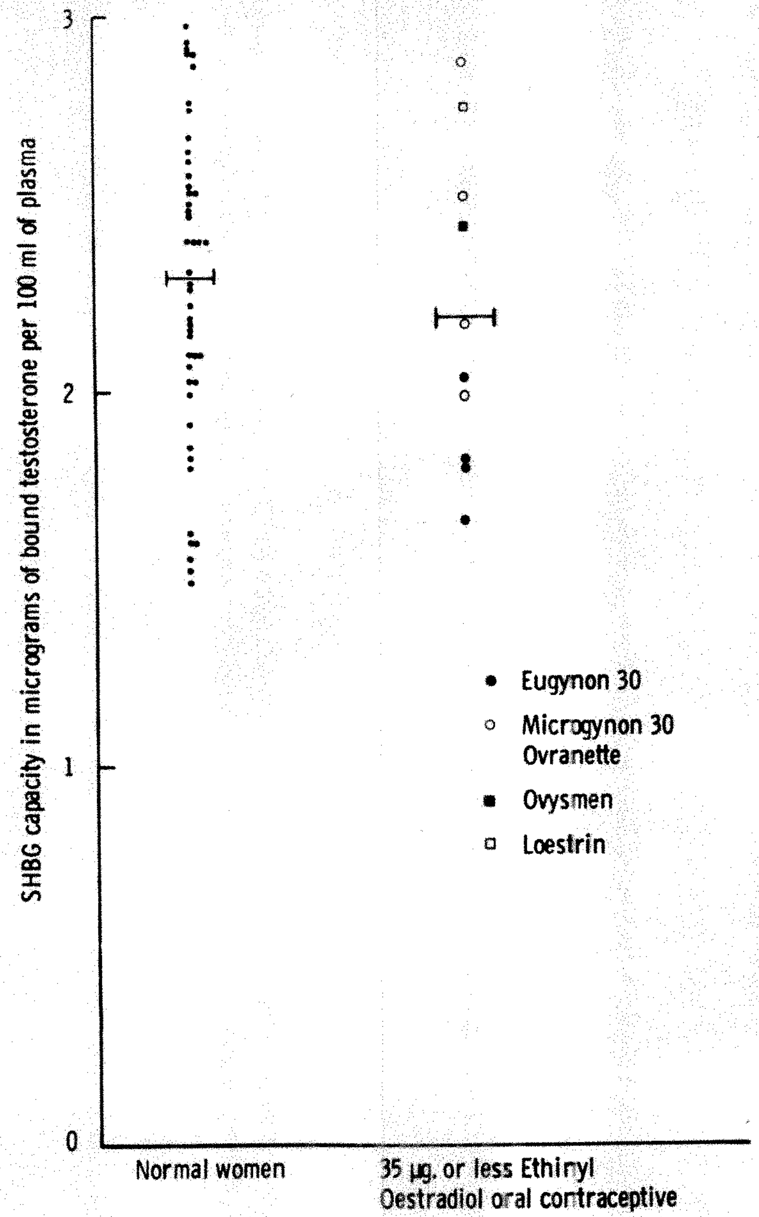

FIG. 2

On the left are depicted the individual values for plasma SNBG capacity in the normal women while on the right are the values seen in women taking a combined oral contraceptive containing 35 µg or less of ethinyl oestradiol. The mean values are also shown as horizontal bars. No statistical difference in SHBG capacity exists between the two groups ($p > 0{\cdot}5$).

that the SHBG capacity was significantly enhanced in women on an oral contraceptive containing 50 µg of ethinyl oestradiol, whilst the SHBG capacity in women taking a pill containing 35 µg of ethinyl oestradiol or less was indistinguishable from that seen in normal ovulating women, even though the dose of progestogen in the 50 μg pill tended to be higher than that of the 30 μg pill.

These results suggest that the oestrogenization of women on a pill containing 50 μg of ethinyl oestradiol considerably exceeds that seen in normal women. However, it could be argued that the increased binding capacity seen in women on the 50 μg pill would significantly reduce the amount of free oestrogen and thus probably substantially reduce its effective biological activity. It could therefore follow that this might go some way to prevent an increase in cardiovascular disorders in women on the 50 μg oral contraceptive.

Another aspect of SHBG capacity in women on oral contraceptives which merits consideration is the availability of endogenous androgen. Testosterone has a three times higher affinity for SHBG than oestrogen (Anderson, 1976). As testosterone binds more avidly to SHBG than does oestrogen the free testosterone levels would be depressed. This would tend to reduce libido, an effect that would be theoretically greater in women on the higher dose pill. Therefore it could be argued that the higher dose pill, although more efficacious than the lower dose pill in the treatment of hirsutism, may reduce free testosterone substantially. Whether this is related to the libido problems in patients on the combined pill has not in fact been demonstrated but remains a theoretical possibility.

It must be remembered that substantial alterations in the bound/unbound ratios of the sex steroids may be produced by oestrogen-progesterone combinations containing 50 μg ethinyl oestradiol. In this respect the 30 μg pill must be considered to produce a more physiological effect.

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SEX HORMONE BINDING GLOBULIN CAPACITY AND POSTMENOPAUSAL HORMONE REPLACEMENT THERAPY

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Summary

The sex hormone binding globulin (SHBG) capacity was measured in 26 normal untreated postmenopausal women and 10 postmenopausal women taking different types of hormone replacement therapy. The patients on hormone replacement therapy had significantly higher levels of SHBG than postmenopausal women ($p < 0 \cdot 001$) and also significantly higher levels than 52 normal ovulating women studied previously (Pogmore and Jequier, 1979; $p < 0 \cdot 02$). This suggests that postmenopausal women on hormone therapy are being overtreated.

IT has been suggested that many postmenopausal women on hormone replacement therapy are being overtreated (Hutton *et al*, 1978). Sex hormone binding globulin (SHBG) is a β-globulin produced by the liver, which combines in plasma with both testosterone and the oestrogens (Anderson, 1976). Oestrogen, either in an endogenous or exogenous form, causes SHBG levels to rise (Anderson, 1976). While progestogen and testosterone therapy reduce plasma levels of SHBG (Pearlman *et al*, 1967; Migeon *et al*, 1968; Vermeulen *et al*, 1969; Tochimoto *et al*, 1970; Ruder *et al*, 1971; Forest and Bertrand, 1972; Murray *et al*, 1973). Thus SHBG capacity is an indication of oestrogenization.

It was therefore decided to measure SHBG in two groups of postmenopausal women: one group consisted of untreated women and the other of women on different types of hormone replacement therapy.

METHODS

Patients

The first group consisted of 26 normal untreated postmenopausal women. All of these women were more than one year past the menopause and their ages ranged from 48 to 72 years. None of these subjects had ever received any form of hormone replacement therapy.

The second group consisted of 9 postmenopausal women, again all more than one year past the menopause, and all of whom had been receiving hormone replacement therapy for at least three months. Added to this group was one patient aged 17 years with primary ovarian failure due to Turner's Syndrome. Four of these women were receiving 0·625 mg per day of conjugated equine oestrogens (Premarin, Ayerst Laboratories Ltd.). A further four women were receiving a mestranol-norethisterone mixture (Menophase, Syntex Pharmaceuticals Ltd., UK). One more postmenopausal woman was being treated with a mixture of conjugated oestrogens 0·625 mg and Norgestrel 0·5 mg daily (Prempak, Ayerst Laboratories Ltd.) and a further patient (Turner's Syndrome) was receiving 0·1 mg of ethyinyl oestradiol daily. All patients were on cyclical therapy and all blood samples were taken during therapy, and not during the period when therapy was withheld.

In all patients, blood was taken from a vein in the antecubital fossa and placed in lithium heparin at 4°C. The plasma was separated by centrifugation within four hours of venepuncture and stored at $-20°$ until assayed.

Measurement of SHBG capacity

The method of assay used and the manner of assessing results were those described in our preceding article (Pogmore and Jequier, 1979).

Results are expressed as µg of bound testo-

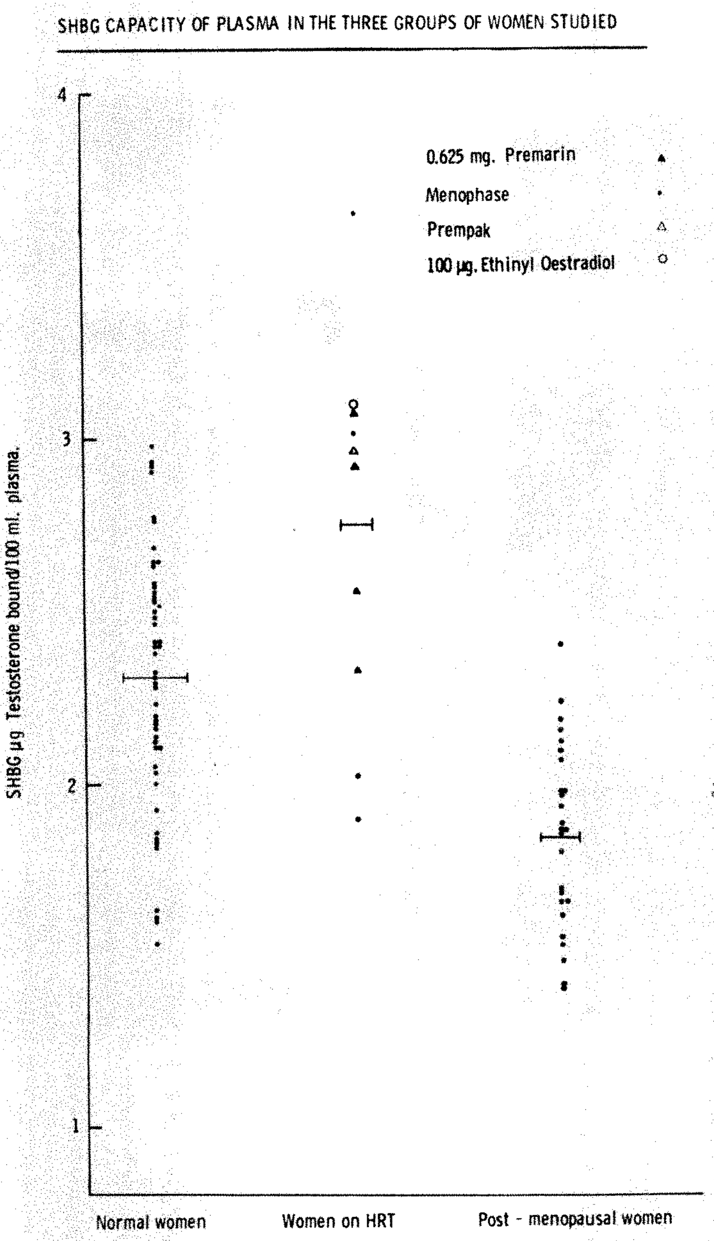

FIG. 1

Individual values of SHBG capacity expressed as µg of testosterone bound/100 ml of plasma. The horizontal bars indicate the mean value in each group.

sterone/100 ml of plasma (μgT/100 ml, Mean ± SEM). An F test was used to test for equality of variances between groups. Student's t test was then used where appropriate to test for the significance of differences between means.

RESULTS

In the 26 untreated postmenopausal women, the mean SHBG capacity was 1·84 ± 0·051 (SEM) μgT/100 ml with a range of values lying between 1·40 and 2·40.

In the 10 treated women, the mean SHBG capacity was 2·75 ± 0·16 (SEM) μgT/100 ml with a range of values between 1·89 and 3·65. Using Student's t test, the levels of SHBG were significantly raised in the treated patients ($p < 0{\cdot}001$) as compared to the untreated postmenopausal patients. As Figure 1 shows, one value for SHBG capacity in the treated group of women is much higher than the others. Even when this value is excluded from the group, the difference between the means of the two groups remains significant ($p < 0{\cdot}02$).

In a previous study (Pogmore and Jequier, 1979) we showed that in 52 normal ovulating women the mean SHBG binding capacity was 2·31 ± 0·05 μgT/100 ml. Statistical comparisons between the untreated postmenopausal women and these normal ovulating women showed that the SHBG capacity was significantly lower in the postmenopausal women ($p < 0{\cdot}001$).

However, if the SHBG capacity levels in treated postmenopausal women were compared with the normal women, the levels of SHBG capacity in the treated women were significantly higher even than those in the normal women ($p < 0{\cdot}02$).

Individual levels of SHBG capacity in each patient are depicted in Figure 1, which also repeats the previously described results in normal women (Pogmore and Jequier, 1979).

DISCUSSION

In our study, sex steroid therapy in postmenopausal women raised the mean SHBG capacity to levels that were significantly higher than those seen in normal ovulating women. This suggests that the dose of oestrogen used was too great to constitute true replacement therapy. This would be in agreement with the markedly elevated oestrone levels that have been found in postmenopausal women undergoing standard replacement regimes (Hutton *et al*, 1978). Nevertheless, some of the values fell within the range seen in the normal women. The wide range of values of SHBG capacity obtained in women on Menophase may be the result of the differing oestrogen content of each tablet at different phases of therapy.

Another aspect of hormone replacement therapy to be considered is androgen activity. As it is known that serum testosterone levels fall in women undergoing the menopause or oophorectomy and that the oestrogen levels also fall substantially under these circumstances (Judd *et al*, 1974*a* and *b*), the rise in SHBG capacity seen in the treated postmenopausal women must be due solely to therapy.

As SHBG has a three times greater affinity for testosterone than for oestrogen (Anderson, 1974), it must be surmised that traditional methods of hormone replacement therapy may produce a substantial fall in the biologically available free testosterone. This may be the explanation for the libido problems suffered by some women on replacement therapy and which may necessitate the addition of androgens to improve sexual drive (Studd, 1976).

The role of progestogens in the alteration of SHBG capacity is less well documented. However, Thijssen and van Kammen (1975) showed that D-norgestrel, lynestranol and medroxyprogesterone, in doses comparable to those used in many replacement regimes, decreased SHBG capacity by some 30 per cent of pretreatment values. However, the SHBG capacity in the five women on combination therapy in this study did not appear to be different from that seen in women on pure oestrogen preparations, which demonstrates the potent effect of oestrogen on SHBG capacity even in the presence of progestogens. Our numbers, however, were too small to be statistically analysed.

This study suggests that some postmenopausal women on traditional methods of replacement are being overtreated with the oestrogens and the use of these preparations, although useful therapeutically, cannot be considered to be true replacement.

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A COMPARISON BETWEEN THE EFFECTS OF NYSTATIN, CLOTRIMAZOLE AND MICONAZOLE ON VAGINAL CANDIDIASIS

BY

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Summary

Nystatin (100 000 units/day for 14 days) and clotrimazole (100 mg/day for 6 days) were equivalent to miconazole (100 mg/day for 14 days or 100 mg twice daily for 7 days) in curing vaginal candidiasis. However significantly more patients relapsed in the nystatin and clotrimazole groups than in either of the miconazole groups.

THE isolation of the polyene anti-candidal agent nystatin from *Streptomyces nursei* reported by Hazen and Brown (1950) was the signal for a therapeutic revolution in the treatment of candidal vaginitis. Although many other polyene antibiotics (e.g. amphotericin B, candicidin and pimaricin) have been isolated none has been proved superior to nystatin which remains in widespread clinical use. In the early 1970's however, the therapeutic armoury for candidal vaginitis was increased by the introduction of two imidazole derivates, namely clotrimazole and miconazole (Holt, 1976).

Odds (1977), in a review of mycologically controlled clinical studies on antifungal drugs used for the treatment of candidal vaginitis, concluded that miconazole and clotrimazole were equally effective and superior to nystatin. His definition of effectiveness was based on the absence of yeasts from a vaginal swab taken within eight days of the end of therapy.

In many studies there has been a tendency to regard the absence of detectable yeasts in the vagina a short time after the end of treatment as evidence of success. However, even the most exhaustive sampling techniques could not be expected to detect all residual viable yeasts. Therefore the success of the treatment should also be judged on the results of further mycological examinations of vaginal swabs taken several weeks after the first post-treatment swab (Turner, 1978). At this time any undetected residual candida will have had the opportunity to re-establish itself.

That this fact has not been generally recognized is reflected in the paucity of studies with such follow-up data. Odds (1977) has found, on analysis of available studies, a significant difference in relapse rates between patients treated for less than 11 days and patients treated for 11 to 23 days.

The approach taken by Odds (1977) to combine data from different studies provides valuable pointers. It is, however, possible that bias could enter the data due to heterogeneity in the trial conditions. Ideally treatments should be compared in the same study under relatively stable conditions. Such a comparative study should include at least two post-treatment mycological follow-ups separated by several weeks.

The present study compares the three most widely used treatments for candidal vaginitis under the conditions described above and reports a mycologically controlled clinical study comparing the manufacturers recommended course of clotrimazole, miconazole and nystatin. In addition a group of patients receiving one miconazole pessary night and morning for 7 days were included. Most of the patients had two follow-up examinations at two and eight weeks after the end of treatment.

METHODS

Patients from three centres entered the study. Centres 1 and 3 were Obstetric and Gynaecology units and centre 2 was a Family Planning Clinic. The entry criterion was the detection of yeasts in the vagina based on their identification in a Gram-stained vaginal smear and the growth of yeasts from a high vaginal swab. Generally speaking most of the patients were symptomatic; however, asymptomatic obstetric patients who had clinical evidence suggestive of candidiasis but did not complain of symptoms were included if mycologically positive. Some pregnant patients noted to have excessive discharge and subsequently shown to have candidal vaginitis were also included. Patients beyond the 30th week of pregnancy were not included.

At the first visit a history was taken and direct questions were asked about factors predisposing to candidal vaginitis (pregnancy, oral contraceptives, diabetes and steroid or antibiotic therapy). Clinical examinations were made at each visit and the presence of vulvitis, vaginitis, cervicitis and discharge were noted and graded as mild, moderate or severe.

Patients were then given their medication in randomly allocated sealed envelopes containing the treatment-packs. The nature of the medication was unknown to the investigator at this time. Differences in the form and duration of therapy made further 'blinding' of the study impractical. In centres 1 and 2 the patients were randomly allocated to treatment with either (a) miconazole nitrate (100 mg) pessaries—one to be inserted nightly for 14 consecutive days; (b) miconazole nitrate (100 mg) pessaries—one to be inserted night and morning for 7 con-

TABLE I
Characteristics of patients

Treatment	Centre	No. of patients	Median age (and range)	Incidence of previous thrush infection (per cent)	Predisposing factors (per cent)*					
					Pregnant	Oral contraceptive	Diabetes	Steroid	Antibiotics	None
Nystatin	3	14	25·5 (19–47)	40	67	6				28
Clotrimazole	1	26	21 (17–31)	12	100					
	2	15	24 (16–36)	20		80	20			20
	3	19	22·5 (17–36)	47	73	13			20	
	Total	60	24 (16–36)	23	62	25	4		5	4
Miconazole (7 days twice daily)	1	26	23·5 (17–36)	4	100					
	2	11	24 (17–56)	27		54			9	36
	Total	37	23 (17–56)	11	70	16			3	11
Miconazole (14 days)	1	21	24 (18–34)	16	100					
	2	11	22·5 (15–30)	27		45	9	18		27
	3	18	25·5 (19–47)	40	67	6				28
	Total	50	26 (15–47)	27	66	12	2	4		16

* Some patients had more than one predisposing factor.

TABLE II

Mycological examinations

	Time to first control examination (days)		First control			Time to second control examination (days)		Second control		
				Negative					Negative	
Treatment	Median	Range	Positive	No.	Per cent	Median	Range	Positive	No.	Per cent
Nystatin	21	17–52	1	13	93	42	31–76	6	7	54
Clotrimazole	28	6–120	7	50	88	42	12–180	17	35	67
Miconazole (7 days twice daily)	28	26–90	5	30	86	42	14–200	1	28	96
Miconazole (14 days)	28	14–120	5	48	91	42	21–90	1	45	98

secutive days or (c) clotrimazole (100 mg) vaginal tablets—one to be inserted nightly for 6 consecutive nights. Centre 3 included a group of patients treated with nystatin (100 000 units) pessaries one inserted nightly for 14 consecutive nights instead of the 7-day miconazole group.

Concomitant anticandidal medication was not allowed and any patient who had received anticandidal medication for the current episode of candidal vaginitis was excluded from the study. Non-pregnant patients were advised to continue the therapy uninterrupted should menstruation occur during the treatment period. No specific recommendations about hygiene or sexual intercourse were made in the protocol.

A second examination of the patient was made approximately four weeks after the start of treatment and a third examination was made after a further six weeks.

RESULTS

A total of 166 patients entered the study; of these 161 returned for at least one post-treatment visit. On breaking the code, 14 were in the nystatin group; 60 in the clotrimazole group; 50 in the 14-day miconazole group and 37 in the 7-day miconazole group. Most of the patients from centres 1 and 3 were pregnant. The main predisposing factor in centre 2 was the use of oral contraceptives. With this exception the centres and treatment groups were well balanced with respect to age and previous history of candidal vaginitis (Table I). Altogether 141 patients (88 per cent) had a predisposing factor. Of these patients, 106 (75 per cent) were pregnant and 27 (19 per cent) were taking oral contraceptives.

TABLE III

Relapse rate

Treatment	No.	Per cent
Nystatin	6/12	50
Clotrimazole	13/46	28·3
Miconazole (7 days twice daily)	1/29	3·4
Miconazole (14 days)	1/41	2·4

Thirty-five patients (23 per cent) gave a previous history of candidal vaginitis.

All patients were positive for candida at the start of treatment. The numbers of patients who remained positive at the first and second control examinations are given in Table II. The cure rates at the first control were statistically comparable ranging from 86 per cent (for 7-days of miconazole therapy) to 93 per cent (for nystatin therapy). However, at the second control (see Fig. 1) there was a much wider gap, the apparent cure rate ranging from 54 per cent (for nystatin) to 98 per cent (for 14-day miconazole therapy). None of the differences were

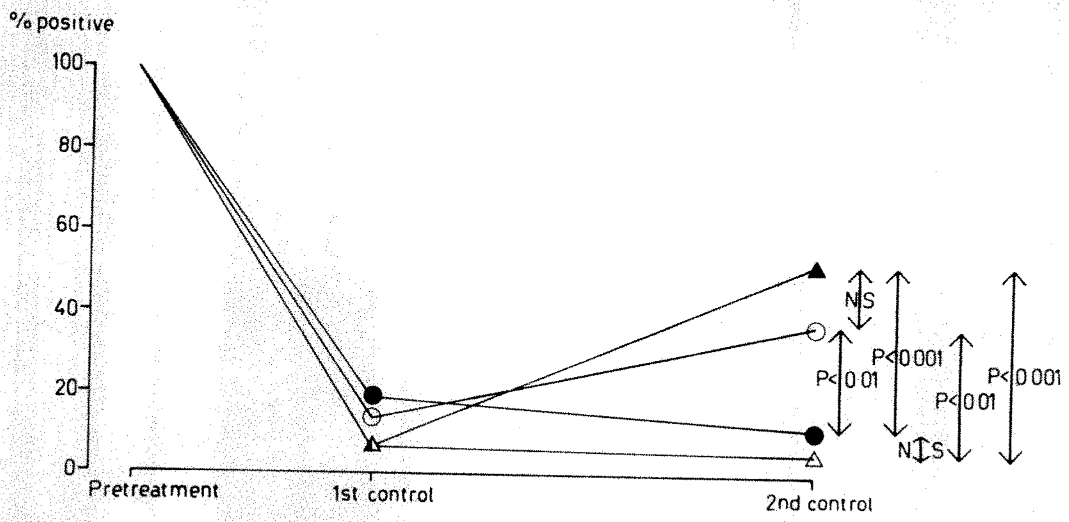

FIG. 1

Percentage of patients positive for candida. Key: ▲—nystatin; ○—clotrimazole; △—miconazole (7 days twice daily); ●—miconazole (14 days).

statistically significant (χ^2 test) at the first control whereas the differences between each of the two miconazole groups and the nystatin and clotrimazole groups were statistically significant at the second control ($p < 0{\cdot}01$). Other differences were not statistically significant.

Although primary cure rates were comparable, nystatin and clotrimazole appear to have a much higher relapse rate than either of the miconazole treatment regimens. However, as some patients were not re-examined at the second control (due either to default or to being treated with different antifungal agents because of the failure of the first course of treatment) these figures may be distorted. For this reason it is necessary to look at the 'true relapse' rates. 'True relapse' was defined as the percentage of patients seen at the second control examination who had become positive for candida having been negative at the first control.

The combined 'true relapse' rates for the four treatments are shown in Figure 2. The difference between both the miconazole treated groups and the clotrimazole and nystatin treated groups was statistically significant ($p < 0{\cdot}01$; χ^2 test). None of the other differences were statistically significant. Of the 166 patients examined, 20 were asymptomatic pregnant patients who had clinical candidiasis. The percentages of patients with the various signs before treatment is shown in Figure 3 which also shows the number of patients who were negative for candida and still had symptoms after treatment.

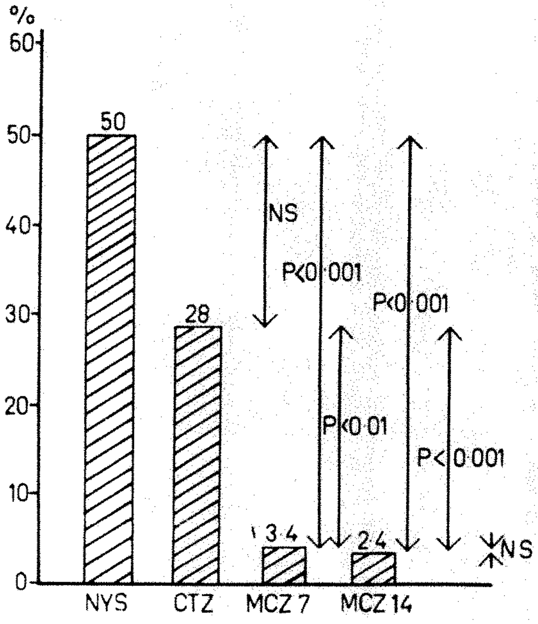

FIG. 2

Relapse rates. Key: NYS—nystatin; CTZ—clotrimazole; MCZ 7—miconazole (7 days twice daily); MCZ 14—miconazole (14 days).

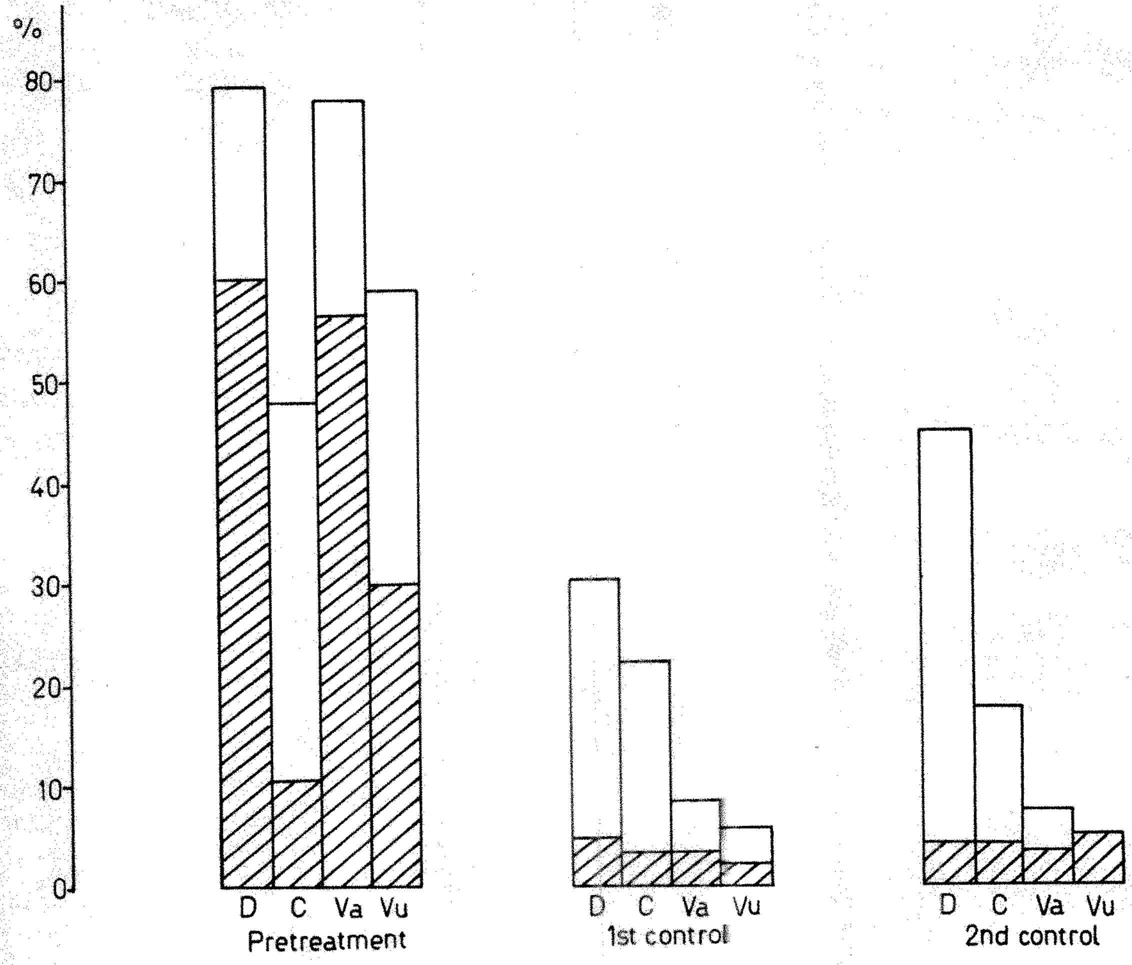

FIG. 3

Percentage of patients with signs before treatment and with signs after treatment at first and second control when patients were negative for candida. Key: □—mild signs; ▨—moderate/severe signs; D—discharge; C—cervicitis; Va—vaginitis; Vu—vulvitis.

COMMENTS

The words relapse, recurrence and reinfection as applied to candidal vaginitis deserve better definition. Recurrence is the general term which should be applied to the reappearance of the condition in women who were thought to be cured.

We chose to call all recurrences which were detected at the second control examination (approximately two months after the end of treatment) relapses rather than reinfections.

Thus, 1400 mg of miconazole nitrate administered as either one 100 mg pessary nightly for 14 successive nights or as one 100 mg pessary night and morning for 7 successive days gave a significantly ($p < 0\cdot001$) lower relapse rate of 3 per cent compared to 28 per cent for 100 mg clotrimazole given for six days.

As measured by minimum inhibitory concentration (MIC) miconazole and clotrimazole are equally active. Holt (1972) gave MIC values for both drugs in the range 0·1 to 10 μg/ml with most isolates inhibited by 0·1 to 0·5 μg/ml. Minimum cidal concentrations were at the higher end of this range. Thus it is not possible to explain the observed clinical differences on the basis of this laboratory data. More recently, however, De Nollin and Borgers (1976) reported fungicidal effects of miconazole on *Candida albicans* at 50 μg/ml (10^{-4} M) which were not present with clotrimazole at similar dose levels and this could explain the differences we observed between treatment with miconazole and clotrimazole.

Miconazole also appeared to be better than nystatin in preventing relapses (3 per cent compared to 50 per cent; $p < 0\cdot001$) even though MIC values for nystatin against yeasts are comparable to those cited previously for miconazole (Van Cutsem and Thienpont, 1972).

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ACUTE LEUKAEMIA RELAPSE PRESENTING AS OVARIAN TUMOUR

BY

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Summary

Relapse of acute lymphoblastic leukaemia is described in a woman with a leukaemic ovarian tumour from which reseeding of the bone marrow had occurred. It is proposed that irradiation of the ovaries with the initial leukaemic therapy may prevent this form of relapse.

CARCINOMATOUS matastases to the ovary are common and leukaemic involvement of the ovary may be found at autopsy in about one-third of women dying from leukaemia (Lucia *et al*, 1952). However, the finding of a large ovarian tumour due to leukaemia, while the patient is apparently in clinical and haematological remission, is very unusual.

CASE REPORT

A 35-year-old Asian female presented with a painful lower abdominal mass which had been present for about three weeks and which was gradually increasing in size. Five years previously she was found to have acute lymphoblastic leukaemia (haemoglobin 4·8 g/dl, white cell count $32 \cdot 7 \times 10^9/1$, 65 per cent blast cells, platelet count $80 \times 10^9/1$) and was treated according to the UKALL II protocol which consisted of the following: Remission induction with vincristine, prednisolone and asparginase. Prophylactic irradiation to the skull and spinal cord and intrathecal methotrexate. Alternate courses of 6 mercaptopurine and methotrexate and monthly injections of cytostine arabinaside for two years. Complete clinical and haematological remission was achieved and maintained until this presentation. The menstrual cycle was regular and normal and she had two children aged 13 and 14 years.

The patient was obviously in some discomfort but otherwise appeared fit. There was a hard, irregular and fixed mass arising from the pelvis about the size of a 20 week pregnancy. The peripheral blood count was normal (haemoglobin 11·5 g/dl, white cell count $5 \cdot 7 \times 10^9/1$, platelet count $275 \times 10^9/1$) but a bone marrow aspirate revealed 8 per cent blast cells.

Examination under anaesthesia confirmed the previous findings. In addition, the uterus was felt to be of normal size and was anteverted and immobile; the cavity was regular and normal-looking endometrium was obtained on currettage. At laparotomy, the abdominal wall was unusually vascular and the parietal peritoneum was thickened. A moderate volume of clear, green fluid was found in the peritoneal cavity and there was a solid, irregular and fixed mass which originated in the left ovary and completely occluded the pelvis. This extended almost to the level of the umbilicus. There were dense adhesions to the parietal peritoneum which was markedly indurated and the omentum was also thickened by tumour involvement. The liver, spleen, stomach and large bowel felt normal but there were enlarged paraaortic lymph nodes. Removal of the tumour was not possible and biopsies were taken from the tumour and omentum. Postoperatively, there was an ileus but this resolved within 48 hours.

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Histological examination of the biopsies revealed infiltration by poorly differentiated round cells, many with prominent nucleoli and, in the ovarian biopsy there was a prominent streaming effect between dense reticulin fibres (Fig. 1) The appearances were compatible with recurrence of acute lymphoblastic leukaemia.

The abdomen and pelvis were irradiated to 1500 and 2500 rads respectively and this was followed by chemotherapy with vincristine, cytosine and prednisolone. Despite satisfactory regression of the tumour mass so that it was no longer palpable, the patient's condition gradually deteriorated and she died 11 weeks after the laparotomy.

DISCUSSION

The presentation of a relapse of acute lymphoblastic leukaemia by a large ovarian tumour has not been reported before. Although Lucia *et al* (1952) found that in 36 per cent of women who died from acute leukaemia the ovaries were infiltrated by leukaemic cells and Lathrop (1967) found a similar (32 per cent) proportion of ovarian involvement in a series of women with lymphosarcoma. The unusual feature in this case was that the patient was thought to have been in remission for almost five years. Initial leukaemic infiltration of the ovaries may have served as a sanctuary from which the cells proliferated and reseeded the bone marrow after cessation of chemotherapy. Similar testicular relapse of leukaemia has been reported in boys (Eden, 1978).

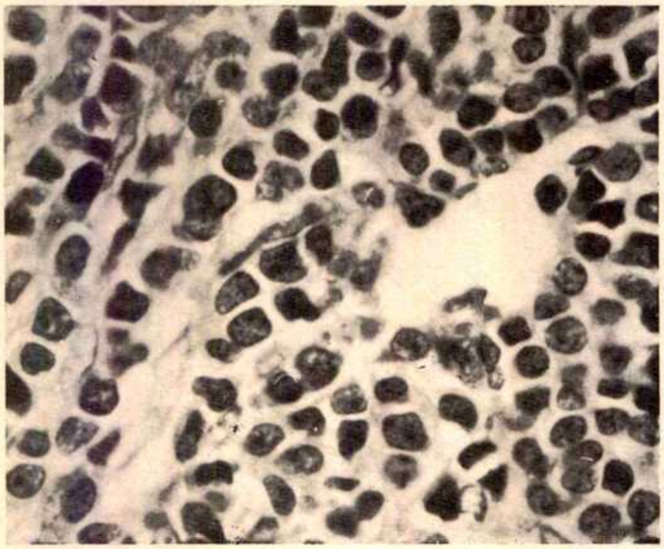

FIG. 1
Histology of ovarian biopsy showing poorly differentiated round cells and prominent streaming effect between reticulin fibres (haematoxylin and eosin × 500).

It is surprising, however, that the peripheral blood count remained normal despite the large volume of leukaemic tissue in the ovarian tumour. Blast cells were only evident in the peripheral blood nine weeks after the operation, when the ovarian mass was no longer palpable, which suggests that they originated from the bone marrow. It is possible that prophylactic irradiation of the ovaries in adult females with acute lymphoblastic leukaemia might prevent subsequent relapse caused by reseeding of the bone marrow. We suggest that this procedure should be considered as, with the steadily improving results of leukaemic therapy, the phenomenon described may appear more frequently in the future.

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PRENATAL ULTRASOUND IN THE DIAGNOSIS AND MANAGEMENT OF FETAL EXOMPHALOS. CASE REPORTS

BY

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Summary

A patient is presented in whom ultrasonic examination at 39 weeks detected fetal exomphalos with an intact sac and no associated gross abnormalities. These findings served as major indications for the safe delivery by Caesarean section of a baby that survived and had successful corrective surgery when 6 months old. The infant might well not have survived vaginal delivery.

MANY gross congenital malformations can now be diagnosed prenatally at ultrasound examination. Two recent reports have described gray scale ultrasound findings in gastroschisis, (Grossman *et al*, 1978; Lee and Warren, 1977) but less information is available for the more common condition, exomphalos (Garrett, 1979). Recent advances in management have improved the prognosis of this condition (Mahour, 1976), yet little precedent exists for how prenatal ultrasound diagnosis might influence obstetric management.

A patient with fetal exomphalos is presented in whom findings on prenatal gray scale ultrasound examination led to Caesarean section at term, a live baby with intact peritoneal sac and a successful outcome despite premature separation of the cord.

CASE REPORT

The patient was a 21-year-old secundigravida, her previous pregnancy in 1974 having ended in a spontaneous vertex delivery of a normal boy of unknown birth weight who was subsequently adopted.

The present pregnancy was complicated by low grade hypertension throughout, leading to hospital admission at 39 weeks gestation. The head was found to be high and deflexed at this time and ultrasound examination was requested to exclude placenta praevia.

The ultrasound study (Commercial water delay OCTOSON, Ausonics Pty. Ltd., Mans Road, Lane Cove, Australia) showed a single 39 week fetus, head presenting (Figs. 1 and 2). The placenta was on the right uterine wall and the volume of amniotic fluid was normal. A presumptive diagnosis of exomphalos was made on the finding of an anterior fetal abdominal wall defect, a shallow abdominal cavity and an exomphalos sac.

In view of these findings and the apparent absence of other associated gross abnormalities on ultrasound, a Caesarean section was done at term from which the mother made an uninterrupted recovery. The infant was a live male weighing 2980 g. As the child was lifted gently from the uterus, the cord, under minimal tension, separated spontaneously from its insertion into the exomphalos. The Apgar score was 6 at one minute and improved rapidly.

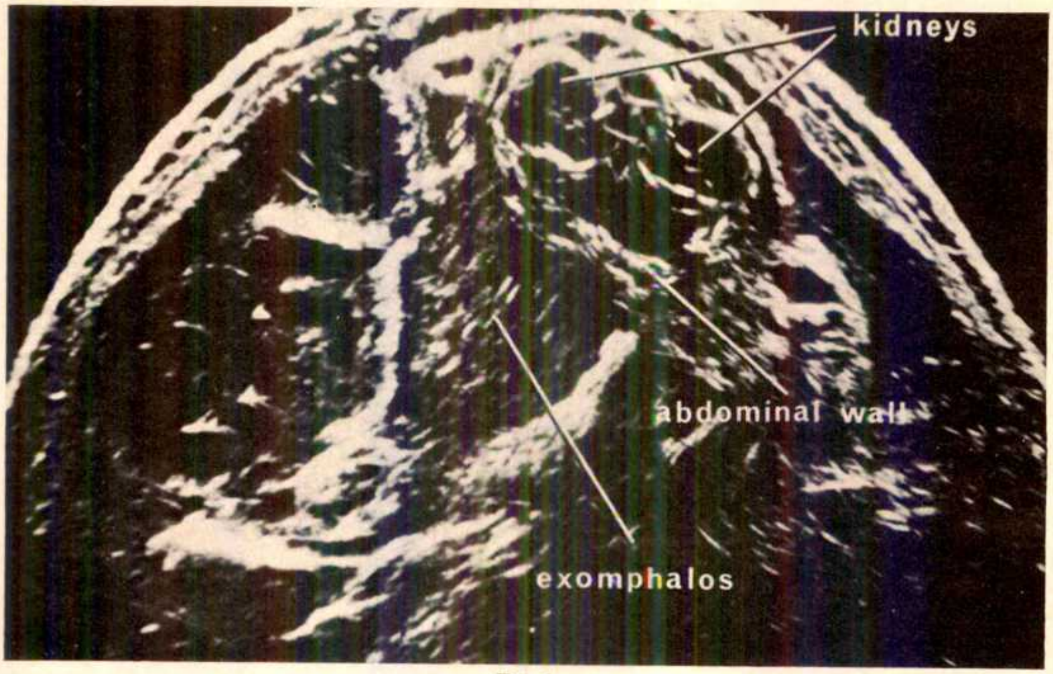

FIG. 1

Transverse section at level of fetal kidneys showing a relatively shallow abdominal cavity, an intact anterior abdominal wall and exomphalos sac.

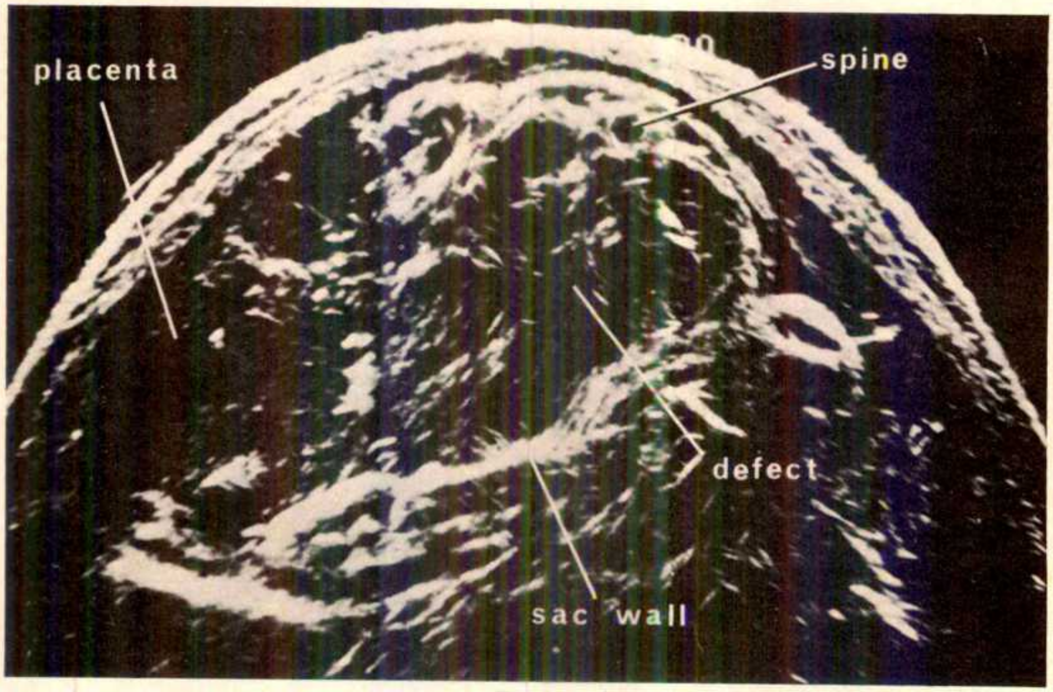

FIG. 2

Transverse section 2 cm below Figure 1. The section is made through the defect in the anterior abdominal wall.

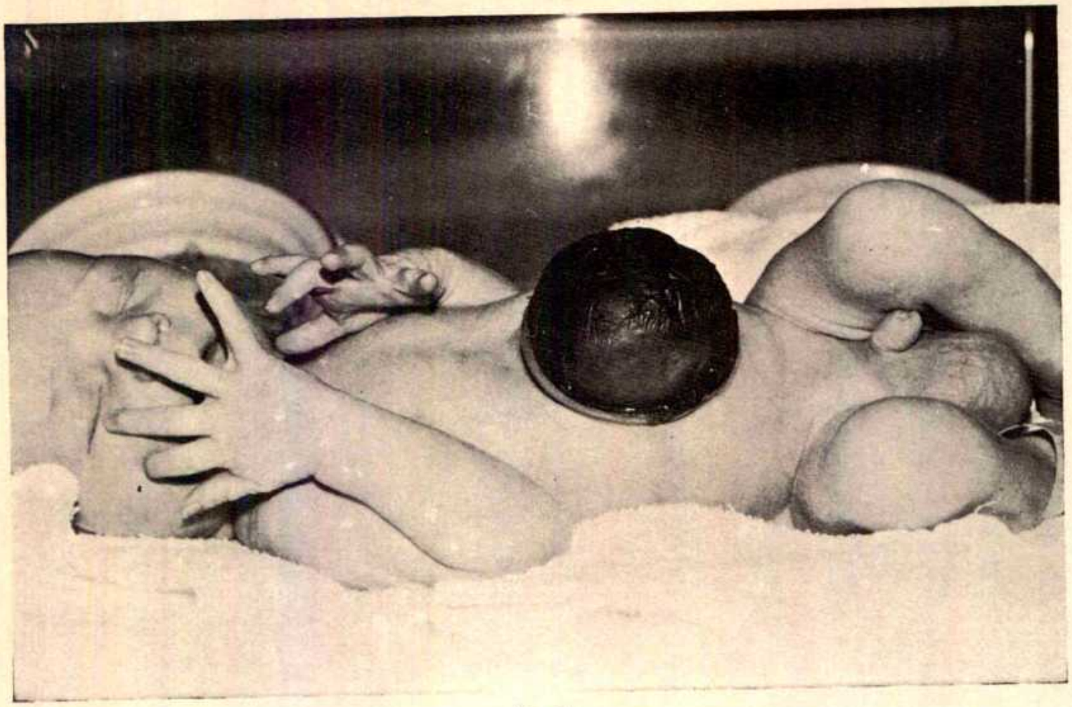

FIG. 3

Exomphalos and right inguinal hernia one week after delivery.

The diameter of the abdominal wall defect was 6·5 cm and that of the exomphalos sac which contained liver and bowel was 19 cm. The only associated abnormalities were bilateral inguinal herniae (Fig. 3). The repair of the inguinal herniae and closure of the sac were deferred for six months at which time the sac was relatively much smaller. The child made an uneventful recovery from this successful operation.

DISCUSSION

The diagnostic features seen on the ultrasound examination were a defect in the anterior abdominal wall, a shallow abdominal cavity, and an extra-abdominal sac filled with abdominal contents. The upper and lower levels of the abdominal wall defect were readily defined. The smooth contour of the sac suggested a diagnosis of exomphalos with an intact sac rather than gastroschisis (Lee and Warren, 1977; Grossman *et al*, 1978). The distinction is important as associated malformations are uncommon in gastroschisis, insertion of the cord is usually not affected and early surgical treatment is indicated.

The prognosis of an exomphalos depends on the size of the defect, whether or not the sac remains intact and on the nature of associated malformations (Mahour, 1976). The problem in obstetric management raised by the prenatal diagnosis of exomphalos was whether or not to do a Caesarean section. Abdominal delivery was finally chosen because it seemed to offer the best chance of maintaining an intact sac and because of the absence of other abnormalities. The degree of maternal hypertension and the high deflexed fetal head assisted this decision. As it happened, vaginal delivery might well have proved fatal for the fetus because the umbilical cord would probably have separated prematurely from its tenuous insertion into the exomphalos sac. Up to half the infants with exomphalos are stillborn (McKeown *et al*, 1953) and about the same number have associated abnormalities (Mahour, 1976). The results of the ultrasound examination, particularly the normal head, heart, renal, gut and bladder outlines suggested that there were no associated abnormalities and save for bilateral inguinal herniae, this was true. The infant having had successful surgery has a good prospect of leading a normal life.

ADDENDUM

Since writing the preceding case report, we diagnosed fetal exomphalos with an intact sac associated with gross hydrocephalus and hydronephrosis during an ultrasound examination at 28 weeks. Because of the multiple abnormalities vaginal delivery was allowed. The child was stillborn and all the ultrasound findings were confirmed at autopsy.

ACKNOWLEDGEMENTS

We acknowledge the technical assistance of Mrs Pam Craig and the help of Dr Ian Hufton.

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CONCURRENT SQUAMOUS CELL CARCINOMA OF THE CERVIX AND PENIS IN A MARRIED COUPLE

BY

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Summary

A married couple who developed, concurrently, squamous carcinoma of the cervix and the penis is reported.

THERE are many theories as to the aetiology of carcinoma of the cervix (Anderson, 1976) but the simultaneous occurrence of carcinoma of the cervix in the wife, with carcinoma of the penis in the husband merits reporting.

CASE REPORTS

The husband, born in Ireland, in 1942, had a phimosis and in 1977 developed frequency of micturition. His general condition was satisfactory, and examination of the abdomen and chest revealed no abnormality. There was, however, a tight phimosis with a hard craggy mass of the glans penis. A chest X-ray and intravenous pyelogram were normal. The patient was admitted to hospital early in March 1978. A dorsal slit was performed and a florid mass originating in the corona of the penis and infiltrating the glans was found. The mass was biopsied and histological examination showed invasive squamous cell carcinoma with numerous mitoses. The patient was given a course of external irradiation with a tumour dose of 5500 rads in 16 exposures over three weeks. The lesion did not respond well and in September 1978 he had an amputation of the penis and formation of a perineal urethrostomy. He has remained well subsequently.

The wife was born in Belfast, in 1949 and had married in 1968. She had had two normal pregnancies in 1970 and 1975 which ended in the delivery of healthy infants at term. At the postnatal clinic in 1975 a cervical smear had shown no abnormality. The patient had then taken oral contraceptives until the end of 1977 when she noticed intermenstrual bleeding and an offensive yellow vaginal discharge. The patient was admitted to hospital in March 1978. Her general condition was satisfactory, there was a friable fungating growth confined to the posterior lip of the cervix. A biopsy was taken which showed poorly differentiated squamous cell carcinoma. As the lesion appeared to be confined to the cervix, the patient had a total hysterectomy and bilateral salpingo-oophorectomy, with removal of a cuff of vagina. Post-operatively the pelvis was irradiated, 4250 rads being given in 16 exposures over three weeks. The patient is now well.

Antigens against herpes simplex virus, cytomegalovirus or chlamydiae were not found in either husband or wife. The cold serum lymphocytotoxic antibody levels were normal in both patients.

COMMENT

Reid and Coppleson (1976) in reviewing the epidemiology of carcinoma of the cervix, summarized the evidence that certain males are particularly prone to cause cancer in their coital partners. Martinez (1969), examining the wives of husbands who developed penile cancer, showed that they had a greatly increased incidence of squamous cell carcinoma of the cervix when compared with matched controls. Mintzis *et al* (1978) reported malignant melanomas in spouses but we have been unable to find a previous report of concurrent genital tract squamous cell carcinoma in husband and wife.

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A REPORT OF THE MEETING OF THE BLAIR BELL RESEARCH SOCIETY AT THE ROYAL COLLEGE OF OBSTETRICIANS AND GYNAECOLOGISTS ON 5th FEBRUARY, 1979

Three papers were presented and discussed.

A paper entitled *The Functional Control of Lung Growth in the Fetal Rabbit* was presented by J. S. Wigglesworth on behalf of himself and R. Desai from the Institute of Child Health. They investigated the effects on fetal lung growth of cervical cord transection at different levels (between C1 and C3 and between C5 and C8) and of transection combined with tracheal ligation. They aimed to investigate the hypothesis that normal fetal lung growth requires combined lung liquid secretion and fetal respiratory movements to proceed normally. Operations were performed at 24½ days gestation and the animals were sacrificed at 28½ days. The mean increment in lung DNA from operation to time of examination was 27 per cent in the high cord section group, 48 per cent in the low cord section group and 104 per cent in the sham operated controls but there was no significant difference in the rate of fetal growth or in that of the liver or kidneys. When high cord section was combined with tracheal ligation, the lungs became large and fluid filled showing similar DNA levels to the control animals. They inferred that fetal respiratory movements help to control lung growth by holding lung liquid within the developing lobule and that a nervous mechanism via the phrenic nerve is of major importance in lung development.

Dr D. A. Viniker presented a paper entitled *Cerebral Function Monitor and Intrapartum Fetal Monitoring* on behalf of himself and Mr Bromley from University College Hospital and of Dr Maynard and Dr Cohen from the London Hospital. The cerebral function monitor (CFM), developed by Dr Maynard, records the activity from the brain and has an inbuilt filtering circuit to eliminate the fetal heart's electrical activity. Electrodes are housed in a suction cap 2·5 cm diameter and this can be applied to the fetal scalp in labour. While conventional EEG records produce a mass of paper several kilometres long for each labour, the CFM records a processed EEG at either 6 or 30 cm an hour. The workers showed an association between neurological impairment and alterations of the function of the brain as shown in traces of adults who underwent cortical variations during open heart surgery. Dr Cohen, at Forest Gate Maternity Hospital, made 15 fetal traces. Dr Viniker demonstrated sleep cycles in the newborn. Work was now in progress to relate CFM traces to fetal state in labour to detect the effects of hypoxia on the fetal brain at an early stage.

A paper entitled In Vitro *Corticosteroid Conversion by the Human Placenta, Fetal Membrane and Decidua in Early and Late Gestation* was presented by Dr A. Lopez-Bernal on behalf of himself and Professor Craft from the Royal Free Hospital. Human placental tissue, membranes and decidua were homogenized and incubated separately with several labelled corticosteroids in vitro. The specimens were obtained from early pregnancy (7 to 10 weeks) and late pregnancy (36 to 42 weeks gestation). There was a significantly different conversion of cortisol in the membranes with early pregnancy. The reduction of cortisone to the more biologically active cortisol was performed only in the decidua. Often some activity occurred in the chorion but the workers felt this was due to minute attached decidual fragments. The enzyme activity in relation to the cortical steroid conversions seemed to appear early in pregnancy and the workers considered it unlikely that the tissues investigated contributed to any acute changes in the corticosteroid levels in fetal compartments or in amniotic fluid at the end of gestation. Trophoblastic tissues (placenta and chorion) tended to oxidize 11β-hydroxysteroids while the decidua had both oxidative and reductive capacities.

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BOOK REVIEWS

Clinics in Obstetrics and Gynaecology, Vol. 5—Neuroendocrinology of Reproduction. Edited by J. E. Tyson. Pp vii+254 with figures and tables. W. B. Saunders Company Ltd, Eastbourne, 1978. Price: £8.25.

This excellent book contains a series of review papers on selected aspects of reproductive endocrinology. It is difficult to understand why the editor has hidden some of his best contributions behind what to many readers must be a forbidding title. Perhaps the most useful contribution the reviewer can make is to say that the book is very good value for money and on the whole well written, and then to indicate what it contains. There are five chapters on neuroendocrinology, three on hormone-receptor interactions, two on prolactin, one on disorders of the luteal phase, one on hereditary male pseudohermaphroditism and one on infertility in men. The quality of the chapters varies from good to excellent so further recommendation is based more on personal interest than on the intrinsic merit of the papers. The section on gonadotrophin receptors is excellent, readily understandable and includes clinical applications. The chapter on male pseudohermaphroditism by Griffin and Wilson is as authoritative as would be expected from the authors and makes fascinating reading. I recommend this book highly.

H. S. Jacobs

Immunology and Immunopathology of the Human Foetal-Maternal Interaction. By Y. W. Loke. Pp v+328 with figures and tables. Elsevier/North-Holland Biomedical Press, Amsterdam, 1978. Price: $64.50.

This is undoubtedly the best book yet published in this field. By confining itself to human pregnancy and its pathology it is not encumbered by doubtful extrapolations from animal data. Being the work of a single author it is comprehensive in its scope and consistent in its theme. The published literature encompassed is impressive although the veracity of some early (and more recent!) work is so open to question that its citation would be more appropriate in an epitaph. Some data could have been presented more critically, particularly in relation to an immunosuppressive role for alpha-fetoprotein and other pregnancy-associated proteins and the transplacental passage of cells. The author rightly concludes that "unequivocal demonstration of fetal leucocytes in maternal blood remains unconvincing" and yet devotes a whole subsection to the effects of that transfer. The postulated immune role for hCG appears under three separate headings which reflects one of the main interests of the author but is disproportionate in the whole scheme of things. Fetal suppressor cells are discussed but are inexplicably omitted from the section on ontogeny of fetal cell-mediated immunity. Suggested hypotheses for an immune origin for pre-eclampsia do not account for its preponderance in first pregnancies and thus are open to question. None of these comments detracts from the value of this book. Inevitably, since the author submitted this manuscript additional work has been published, some of which may prove to be seminal. Despite this the book can be highly recommended for the immunologist wishing to know more about pregnancy and, given some application, the obstetrician inquiring about pregnancy immunology. The price is the only drawback.

G. M. Stirrat

Obstetrics and Gynaecology. By R. W. Taylor and M. G. Brush. Pp 220 with 27 figs and 4 tables. Baillière Tindall, London, 1978. Price: £2.95.

The authors have produced a book for British undergraduates whose training period has been considerably reduced in recent years and the pattern of teaching has changed. My initial assessment that the authors had succeeded in their attempt was somewhat modified by student comments. The principle readers of this book will be undergraduates so it was interesting to note the views of those students selected to read the book. They felt that the emphasis was on obstetrics, and the gynaecological material was limited. Perhaps more important, they felt that the book would be insufficient for final examinations, always a consideration when students are purchasing books. Providing undergraduates accept that they consult other textbooks in the libraries in those areas they consider necessary for one reason or another, this should not prove a problem. I would certainly recommend it to undergraduates and teachers as a good introductory book. Nevertheless it must be used in conjunction with the information gained during their clinical training and reference to other books from time to time. This is a book which requires to be read on more than one occasion in order to obtain the full benefits from its concise presentation. It contains more information for the undergraduate than appears initially. I have no doubt it will prove to be an asset to undergraduates in this country and also be helpful to overseas doctors who wish to take examinations for limited registration in this country.

V. R. Tindall

Gynecologic Cytopathology: A Color Atlas of Differential Diagnosis. By MARIE LUISE SCHNEIDER and HANS-JOACHIM STAEMMLER. Pp xii+187, with 150 illustrations. W. B. Saunders, Company, London, 1977. Price: £24.50.

THIS book contains 150 photomicrographs illustrating a variety of cytological patterns which may be encountered in Papanicolaou smears of the uterine cervix. The fields selected for photograph are carefully chosen to contrast the morphology of cells shed from the healthy cervix with the appearances of cells shed from infected or malignant cervices. The quality of the photographs in this atlas is very high. Nuclear and cytoplasmic detail is clear and the contrasting colours of the Papanicolaou stain are accurately reproduced. Each photograph is accompanied by an explanatory schematic drawing which is particularly helpful for beginners. The emphasis in the text is on differential diagnosis and a section is devoted to describing degenerative cellular changes due to infection or irradiation. These present particularly difficult problems of diagnosis, as they can easily be confused with malignant cells. Criteria for distinguishing between cells which look alike are listed and a comparison of the sizes of morphologiccally similar cells of different origins are made. Cytometric tables are provided for reference and form a particularly useful appendix to the book. It is disappointing that the authors decided against including a section on hormone cytology on the grounds that it was adequately covered in other books. They have also failed to illustrate the cytology of endometrial aspirates. The photographs of degenerated endometrial cells in cervical or vaginal smears which are included do not adequately reflect the more subtle changes seen in cells aspirated directly from the endometrial cavity. Aspiration techniques are being used with increasing frequency as a means of monitoring the endometrial status of patients receiving hormone replacement therapy and these omissions make this book less comprehensive than one would wish. Finally in a number of places in the text the authors give the impression that microinvasion can be diagnosed from the morphology of exfoliated tumour cells. They fail to appreciate the limitation of the cytological technique and make the assumption that analysis of cells shed from the surface of a tumour reflect the degree of infiltration of tumour. This is an erroneous concept, which has no scientific justification. This book provides an excellent set of photographs which would be useful for teaching or reference. It represents a successful attempt to demonstrate the important entities in gynaecological cytology and as such, can be recommended to the practising cytopathologist.

Dulcie V. Coleman

Pain Relief in Labour. By D. D. MOIR. Pp i+122 with numerous figures and tables. Churchill Livingstone, Edinburgh, 1978. Price: £1.95.

ANY Midwifery Department which does not contain in its library at least one copy of this book must be considered as being sub-standard. Dr Moir has achieved, within the compass of a pocket-sized paperback, a succinct yet highly informative review of the current techniques by which relief from pain and anxiety may be provided for labouring women in the United Kingdom. Aspects of the pharmacokinetics of placental transfer are touched upon briefly yet informatively, and there are well formulated accounts of the maternal and perinatal 'side-effects' of the drugs and techniques. Although the author reveals his own preferences, he sustains a well-balanced presentation throughout. The final Chapter, on the preparation of a patient for general anaesthesia (including observations on diet and on antacid prophylaxis) and on the care of the unconscious patient, is a very well worthwhile addendum to the general text. This monograph is highly commended.

J. Selwyn Crawford

Female and Male Climacteric. Edited by P. A. VAN KEEP, D. M. SERR and R. B. GREENBLATT. Pp v+146 with figures and tables. MTP Press Ltd, Lancaster, 1979. Price: £6.75.

YET another set of conference proceedings—this time the Second International Congress on the Menopause held in Jerusalem in June 1978. But this report is different. Each workshop, which involved several speakers, has been summarized by a moderator so that each chapter contains the more important comments and findings of the contributors. Few data are presented and the report is not intended to add to the main body of scientific information. Rather, it gives the feel of the meeting and enables the non-expert to update his own knowledge. Twelve chapters deal with subjects such as the ageing ovary, the climacteric syndrome, effects and side effects of hormone therapy, the endometrium, blood clotting and so on. The only chapter that is too technical for the general medical reader is on oestrogen and progesterone receptors. The male climacteric occupied only one workshop and was shown to have no endocrinological existence. Almost all the well known investigators of the menopause were present. Here is an opportunity to learn their thoughts without having to wade through their data.

D. B. Paintin

Essential Obstetrics and Gynaecology—A Guide for Postgraduates. By J. Willocks. Pp i+250. Churchill Livingstone, Edinburgh, 1978. Price: £4.25.

The authors states in the preface that this book is intended for postgraduate diploma reading for the MRCOG, and immediately one must say that it is eminently suitable for this. Every one of its 250 pages is crammed with succinct information tidily arranged. A telegraphic style has been avoided and the author is lucid and manages to maintain a sensible balance between established lore and recent advances. Many textbooks embracing the most up to date therapies frequently over-emphasize the latest advances, and thereby risk early obsolescence as new events overtake them. The reader should appreciate that there are no illustrations, thus allowing maximum use of space for information and basic clinical philosophy, which is allied to a sound evaluation of the place of modern technology in obstetrics and gynaecology. The first part is devoted to obstetrics and the second to gynaecology, with a useful small section at the end containing suggestions for further reading and an adequate index. If there is any criticism to be made it is that the author permits reference to individual workers extant in areas perhaps of a contentious nature. Again, I thought there was perhaps a too deprecatory attitude taken towards the place of surgery in gynaecological cancer, and in particular the total omission of the place of combined surgery and radiotherapy in the treatment of carcinoma of the cervix. One is tempted to recall the taunt of the old-time pelvic surgeons, who referred to their accoucheur colleagues across the border as gynaecological physicians. The days of this attitude of rivalry have long since passed. In conclusion, I can thoroughly recommend this comprehensive and up to date little book, which, though aimed at the MRCOG candidate, will, I feel sure, be read with advantage by many more senior practitioners, both in and outside the specialty.

L. Easton

Lower Urinary Tract Function and Dysfunction. By Nabil K. Bissada and Alex E. Finkbeiner. Pp x+270 with figures and tables. Appleton-Century-Crofts, New York, 1978. Price: £32.50.

This book is essentially concerned with the pharmacology of the bladder and urethra—a much neglected area. Some of the subjects have already been covered in a series of articles on uropharmacology which appeared in 'Urology'. The book is divided into chapters on anatomy, neurology, neuropharmacology, investigation, pharmacological treatment, and surgical and mechanical treatment. The chapter on anatomy still refers to the 'base plate mechanism' of the bladder which is no longer widely believed, and to the three layers of the detrusor which in practice are most difficult to identify. The important conclusions of Gosling and Dixon, who are pre-eminent in the field of neuro-anatomy of the bladder and urethra, are scarcely referred to. The neurology and neuropharmacology are amply covered and easy to read. The chapter on investigation falls short of current urodynamic practice: single channel cystometry has many limitations. The discussion on urethral pressure measurement fails to make the point that it is the synchronous difference between bladder and urethral pressures which is important. The pharmacological treatment covers a host of drugs but forms a non-critical review rather than a guide to treatment. The section on surgical management deals with many operations and is well illustrated. The book is extremely well referenced and despite the criticisms made here, it is a helpful addition to any urodynamic library.

S. L. Stanton

Fetal Endocrinology. Edited by T. Zondek and L. H. Zondek. Pp x+158 with 39 figs and 7 tables. S. Karger AG. Switzerland, 1978. Price: $47.50.

This small book is a heterogeneous assembly of writings on fetal endocrinology. It varies from a 15 page scholarly essay by Alfred Jost on the hormonal control of fetal growth to a 4 page snippet by the late John McClure Browne on the effects of hormone administration in pregnancy. Perhaps deliberately, the two best chapters have been put first. Jost's chapter on fetal growth is a pleasure to read; a lucid balanced account from the point of view of a biologist who has contributed much to our knowledge of the subject. I would have regretted that Jost had chosen fetal growth rather than sex differentiation if it were not that Erich Bloch made a good job of writing on this topic in the second chapter. The editors themselves, Lilly and Theodor Zondek, contribute a chapter on the determination of fetal sex which fills out some aspects not covered by Bloch. Not surprisingly, the data on human fetal endocrinology are sparse and most authors have to fill out with animal findings. This is most marked in the section on the hypothalamus-pituitary adrenal axis by Jenkin, McMillen and Thorburn who have systematically examined the pituitary hormones in terms of the findings in rats, sheep, monkeys and man. Although the legwork may indeed be by the junior authors as implied by the order of the names, the style and ideas are unmistakeably Jeffery Thorburn's. A readable book without much reference value. Not comprehensive and seldom profound. It will not last long.

A. Klopper

The Cervix. Edited by J. A. JORDAN and A. SINGER. Pp vii+529 with figures and tables. W. B. Saunders Company Ltd, London, 1978. Price: £20.00.

THIS book was designed by its editors to serve a threefold purpose. It provides in one volume up-to-date information for the clinician on the management of problems related to the cervix, a comprehensive text for students, both undergraduate and postgraduate and, thirdly a source of information for research workers, with details of current research on the cervix. To fulfil these requirements, the book must cover a very wide field, which may seem somewhat of a paradox when it is dealing with one relatively small organ. With 43 chapters grouped into eight sections, the editors have left no facet unexamined and the resulting monograph must more than satisfy their initial aims. Two of the sections deal with the natural history, aetiology, diagnosis and management of premalignant and malignant disease of the cervix in a most comprehensive manner with individual chapters by many contributors, each an acknowledged expert in his subspecialty. This part in itself would make an excellent monograph but other sections deal equally thoroughly with anatomy and morphology, at all levels down to fine ultrastructure, physiology, changes in pregnancy and labour, inflammatory disease and cervical injuries and anomalies. It is profusely illustrated with excellent photographs, photomicrographs and line diagrams and the book is the fullest work on the cervix available. It can be recommended to all whose work involves the cervix; gynaecologists, obstetricians, pathologists and research workers. It must be said, however, that one of the major advantages of the book may, to some readers, be a drawback, in that the meticulous attention to detail and the very full manner in which most of the subject matter is dealt with may be rather overwhelming; perhaps a summary at the end of each chapter would have aided those who need a quick reminder of the contents. This should not, however, be taken as a criticism of a book which is of the highest quality, both of content and presentation.

M. C. Anderson

Diagnostic Ultrasound in Clinical Obstetrics and Gynecology. Edited by H. E. THOMPSON and R. L. BERNSTINE. Pp xii+192 with illustrations. John Wiley & Sons, Chichester, 1978. Price: £17.65, $34.50.

BASED on their experience of 30 000 obstetric and gynaecological ultrasound examinations at Denver, the authors intend to "help the clinician use ultrasound without involving unnecessary engineering and physical details". This aim will be achieved although the elementary clinical introductions to each problem are appropriate for non-obstetric readers, reflecting the common transatlantic practice for clinicians to 'read' or measure sonograms obtained by technicians. While all the established roles of ultrasound in our specialty are included, limitations and difficulties are not discussed adequately and there is insufficient detail on recent concepts and methods relating to major topics including fetal growth retardation. For example, it is suggested that the fetal trunk should be measured in the subdiaphragmatic region where it is "cylindrical for a length of several centimetres"—use of the umbilical vein echoes as a marker to standardize trunk measurements is surely well established. Omission of the recently described technique for ultrasonic monitoring of the ovarian follicular cycle is less surprising than the absence of any mention of fetal breathing studies. The text is liberally illustrated with almost 200 sonograms. These have the merit of realism in that they are presented, without retouching, just as they appeared at scanning; it is unfortunate, however, that superimposed arrows corresponding to structures numbered in the captions have sometimes been placed imprecisely or omitted, and in one picture an ovary is misinterpreted as the uterus. Similarly, there is an obvious artist's error in one of the many very clear diagrams that support an excellent chapter on ultrasound mechanics. The final chapters deal adequately with radiation hazards, and less so with scanning and display technology—real-time imaging is outlined only very briefly. Despite the criticisms noted, this compact and attractive book is a useful primer for clinicians or supporting personnel starting to train in diagnostic ultrasound. However, obstetricians with scanning experience would probably not find value for money.

C. R. Whitfield

Topics in Hormone Chemistry, Vol. 1. Edited by W. R. BUTT. Pp 291 with illustrations. Ellis Horwood, Chichester, 1978. Price: £17.00.

THE book comprises reviews of six topics and it would deserve a place in most physiological libraries if it contained only the authoritative review of gastrointestinal hormones by H. Gregory and P. Sholtes. This complex field is covered under the headings origin and characterization and biological actions. However the usefulness of the book extends beyond this single article. Ectopic hormones by Lesley H. Rees provides an encyclopaedic review in which ACTH and related peptides are covered in particular detail richly illustrated with data from Rees' own work. Insect hormones (K. C. Highnam) is an excellent review and emphasis of similarities between neurosecretory hormones of insects and vertebrates will make this section of interest to scientists from many disciplines. The hormonal peptides of the hypothalamus (S. L. Jeffcoate) together with prostaglandins and uterine function (W. P. Collins and Eve A. Willman) extend the range of the book to two other rapidly developing fields. The problems of measurement of the divers substances in both these groups are emphasized. Discussion of the contribution of recent work on prostaglandins to our understanding of uterine physiology is particularly valuable. Sex hormones of the fungi (B. A. Knights) covers a field which has been opened up during the past eight years by characterization of about ten new substances. All the contributors to this pot-pourri are actively engaged in research in the fields which they review, covering the literature through 1976 and in some instances into 1977. These articles provide a useful source of reference on each of the subjects covered.

P. Mary Cotes

BOOKS RECEIVED BUT NOT REVIEWED

Age at Menopause. By P. C. BRAND. Pp 135 with figures and tables. International Health Foundation, Brussels, 1978.

Research in Human Reproduction: Strengthening of Resources in Developing Countries. Report of a WHO Study Group. Technical Report Series, No. 627. Pp iii+16. WHO, Geneva, 1978. Price: Sw. fr. 4.–.

Clinical Management of the Osteoporoses. By G. S. GORDON and C. VAUGHAN. Pp ix+208, with 35 figs and tables. HM+M Publishers Ltd, Aylesbury, Bucks, 1976. Price: £12.50.

Field Guide to the Detection and Control of Xerophthalmia. By A. SOMMER. Pp 47. WHO, Geneva, 1978. Price: Sw. fr. 10.–.

An Introduction to the National Perinatal Epidemiology Unit and Annual Report for 1978. Pp 36. National Perinatal Epidemiology Unit, Oxford, 1978.

Becoming a Mother. By ANN OAKLEY. Pp 328. Martin Robertson & Co, Ltd, Oxford, 1979. Price: £5.95.

A Growth Chart for International Use in Maternal and Child Health Care. WHO Publication. Pp 35. World Health Organization, Geneva, 1978. Price: Sw. fr. 10–, US$5.00.

Induced Abortion. Report of a WHO Scientific Group. Technical Report Series No. 623. Pp 65 with 2 figs and 12 tables. WHO, Geneva, 1978. Price: Sw. fr. 7.–.

Steroid Contraception and the Risk of Neoplasia. Report of a WHO Scientific Group, Technical Report Series, No. 619. Pp 54 with 10 tables. WHO, Geneva, 1978. Price: Sw. fr. 6.–.

EPH- Gestosis Publication No. 11. Edited by E. T. RIPPMANN and H. STAMM. Pp 373. Organization Gestosis- Press, 1978.

Models of Hemodynamics in Normal Pregnancy and EPH- Gestosis. By B. H. DOUGLAS. Pp 39 with 9 figs. Organization Gestosis- Press, Basel, 1977.

Gerinnung und Fibrinolyse bei ungestorter Graviditat und EHP- Gestose. By S. E. KUNZ. Pp 139 with 62 figs. Organization Gestosis- Press, 1978. Price: Sw. fr. 20.

EPH- Gestose, Ubersicht und Statistische Studien. By G. BARTHEL-WOTTKE and C. GOECKE. Pp 135 with 122 tables. Organization Gestosis- Press, 1978. Price: Sw. fr. 20.

EPH- Gestosis (Pre-eclampsia) Etiology, Prevention and Treatment. By W. B. PATTERSON. Pp 32. Organization Gestosis- Press, 1978. Price: Sw. fr. 10.

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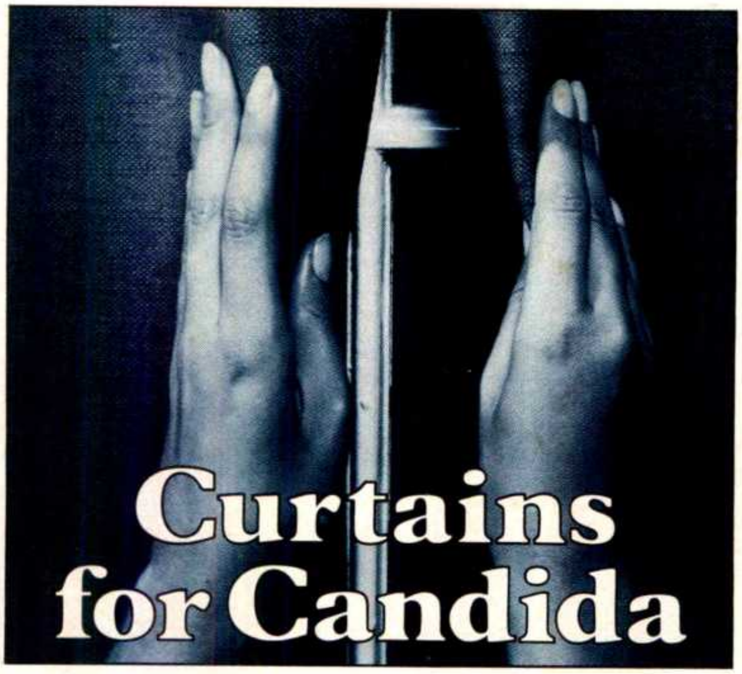

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1. Avram, A. et Grupper, Ch. Bulletin de la Société Française de Mycologie Médicale 1975 Tome IV (2).
2. Preusser, H.J. et al. Research Report 1974. On file Cilag-Chemie.
3. Schweisfurth, R. Research Report 1974. On file Cilag-Chemie.

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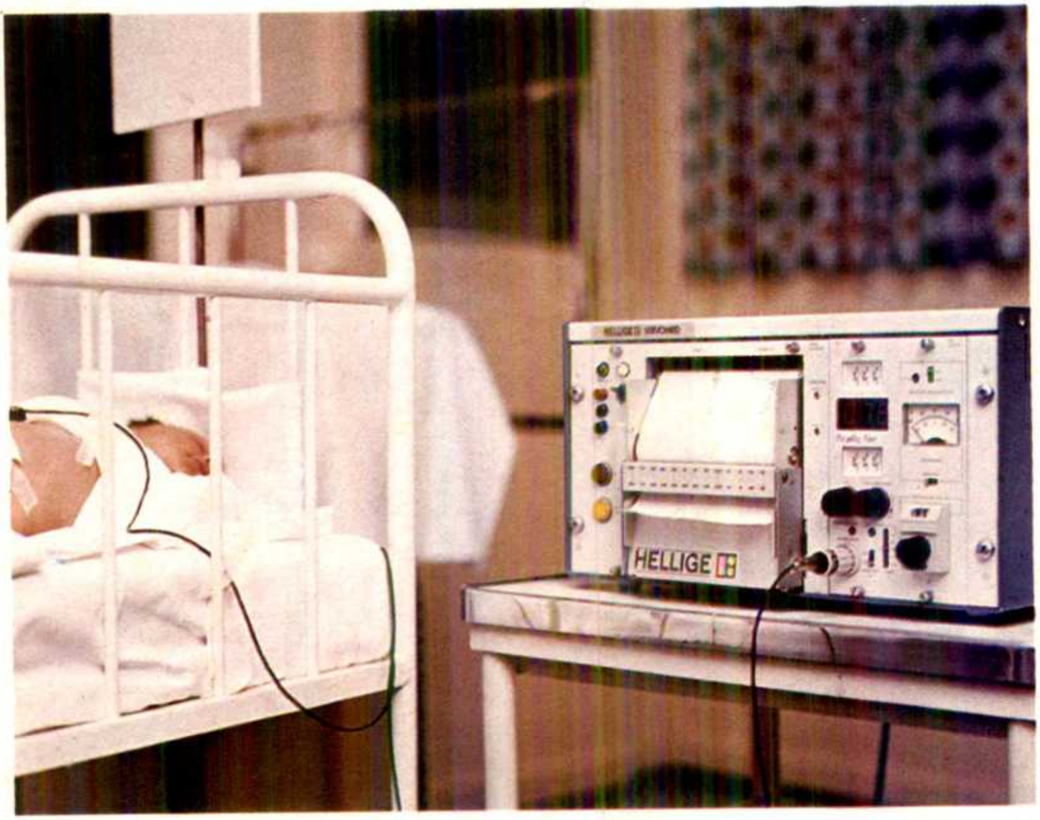

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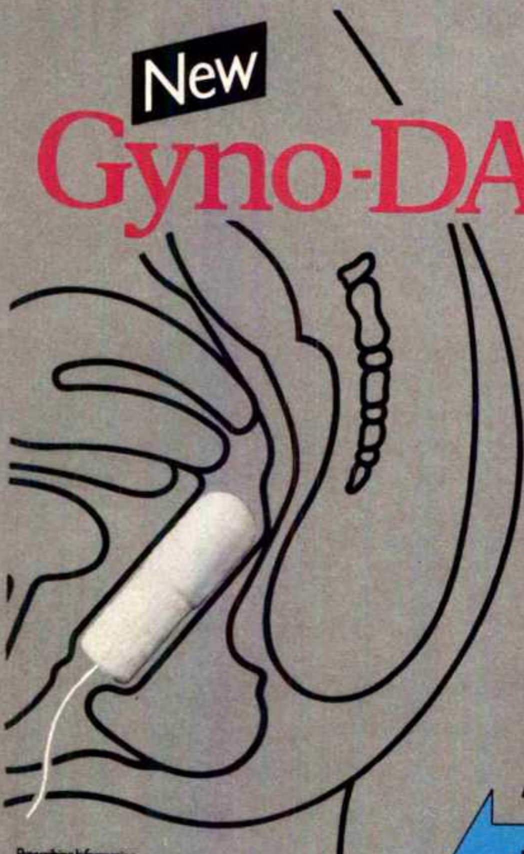

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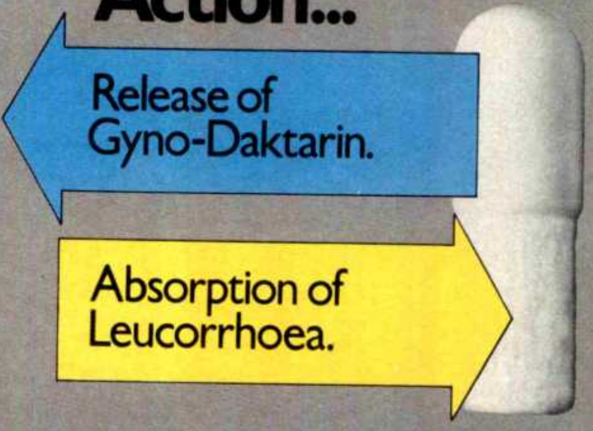

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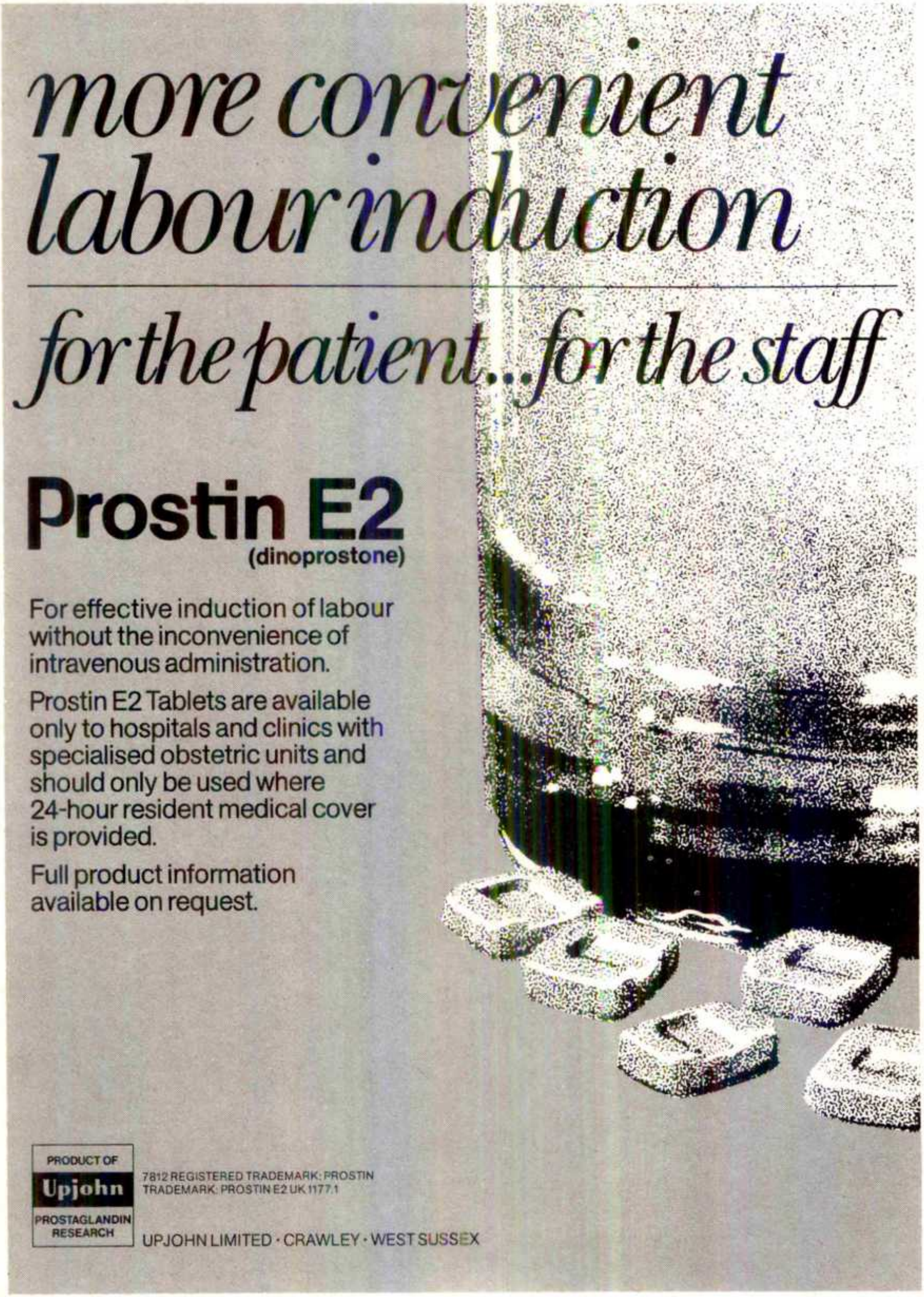

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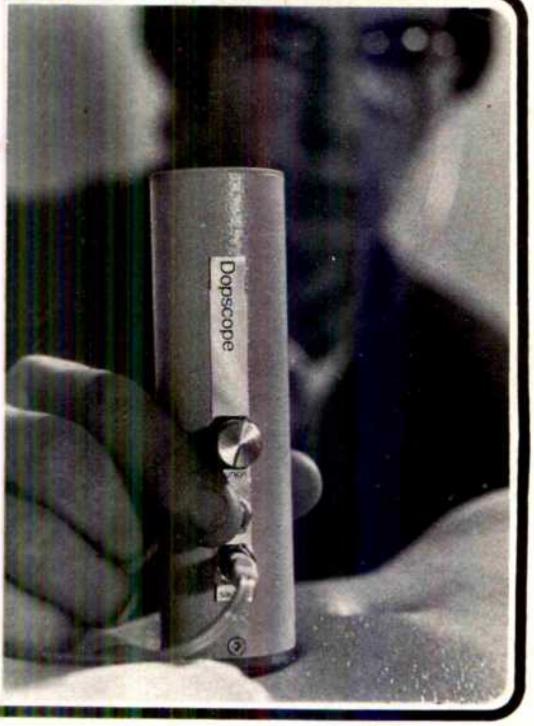

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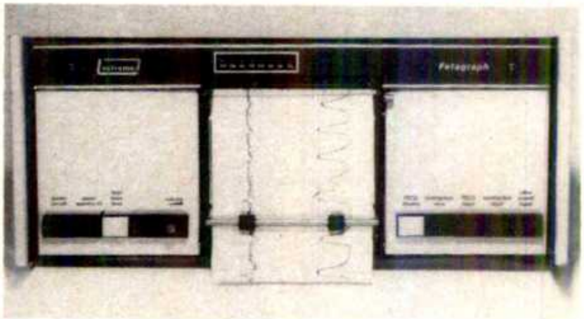

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2. ibid., 101-108. **3.** ibid., 98-100.
4. ibid., 114-123.

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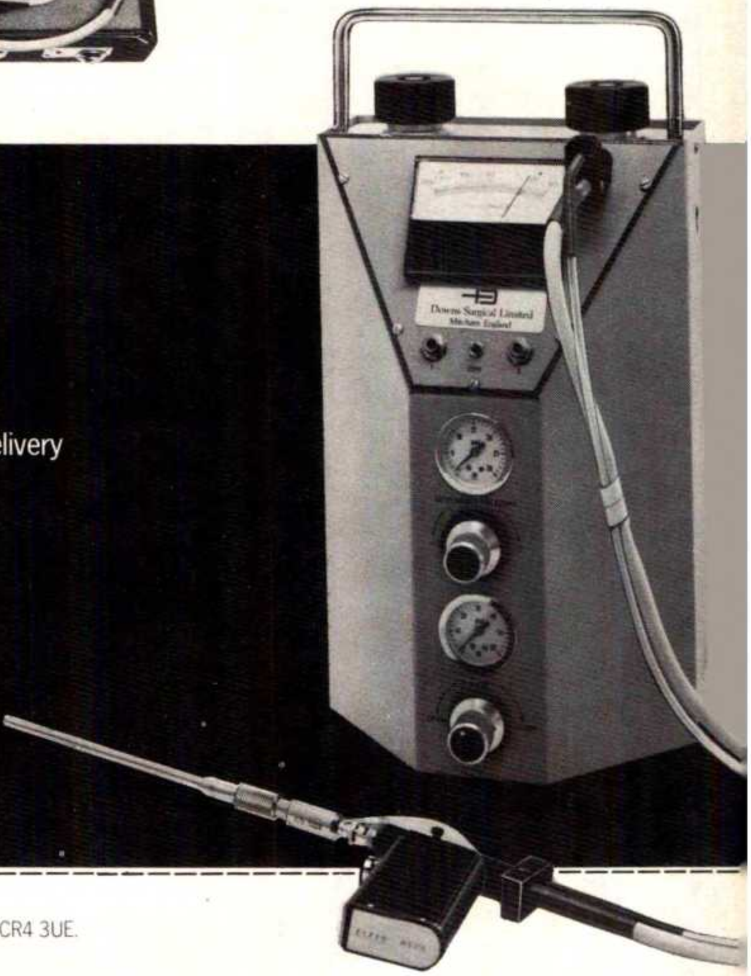

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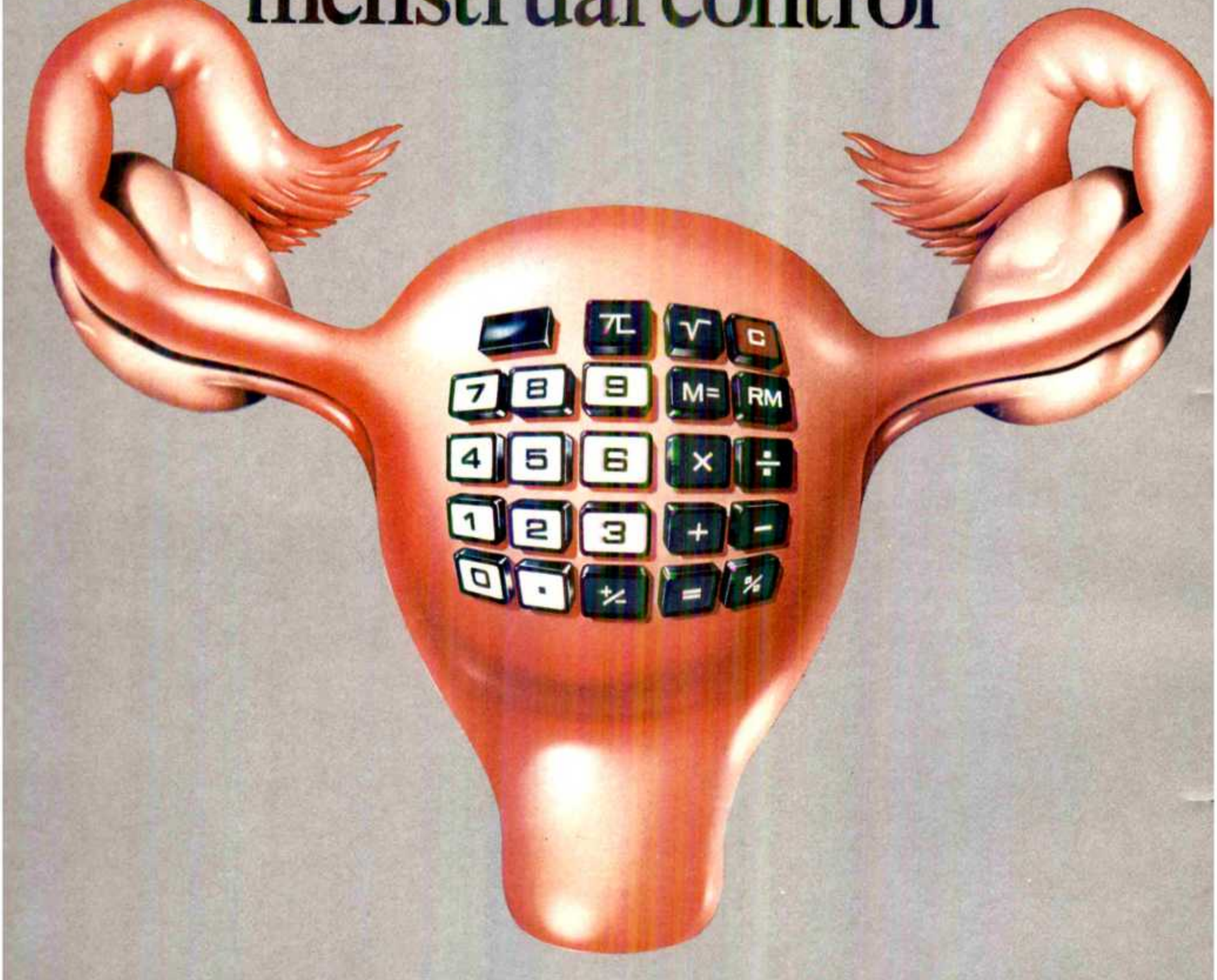

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British Journal of Obstetrics
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Vol 86 No. 8 NEW SERIES AUGUST 1979

FACTORS INFLUENCING THE TREATMENT OF PATIENTS WITH STAGE IA CARCINOMA OF THE CERVIX

BY

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AND

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Summary

A total of 122 patients with Stage Ia carcinoma of the cervix was followed for 5 to 25 years. Eight recurrences were found, four of which were located in the vagina, cervix or the bladder and four on the pelvic wall. Five of the recurrences were detected after 5 years of follow-up. Tumour cells were found in blood vessels or lymphatic channels in eight patients and five of them developed metastases. It is proposed that only tumours with a depth of stromal invasion of less than 5 mm should be treated conservatively. If blood vessels or lymphatic channels contain tumour, we would recommend a Wertheim's hysterectomy or treatment by intracavitary and external irradiation.

Stage Ia carcinoma of the cervix is diagnosed when abnormalities of the cervical epithelium are associated with unambiguous histological evidence of early stromal invasion. The diagnosis should be based upon microscopic examination of tissue removed by biopsy, conization, amputation of the cervix or removal of the uterus. The depth of stromal infiltration and the presence or absence of tumour in lymphatic or blood vessels are currently not taken into consideration in staging.

The recommended treatment for stage Ia (or microinvasive) carcinoma of the cervix ranges from conization to radical surgery and radiotherapy (Averette *et al*, 1976; Benson and Norris, 1977; Bohm *et al*, 1976; Burghardt and Holzer, 1977; Christophersen *et al*, 1976; Duncan and Walker, 1977; Leman *et al*, 1976; Roche and Norris, 1975; Seski *et al*, 1977). The reported frequency of lymph node metastases varies from 0 to 7 per cent, (Benson and Norris, 1977; Bohm *et al*, 1976; Duncan and Walker, 1977; Leman *et al*, 1976; Roche and Norris, 1975; Seski *et al*, 1977). Excellent results are achieved whatever the treatment if five-year survival figures are used as criterion of success. In two previous series from our hospital (Kjørstad, 1977; Kolstad, 1969) it was found that 99 per cent of the patients survived for five years. However, we have seen recurrences after five years and that is what prompted the present study which was undertaken in the hope of clarifying the definition, histology, diagnosis and treatment of State Ia carcinoma of the cervix.

PATIENTS AND METHODS

Figure 1 shows the relative frequencies of

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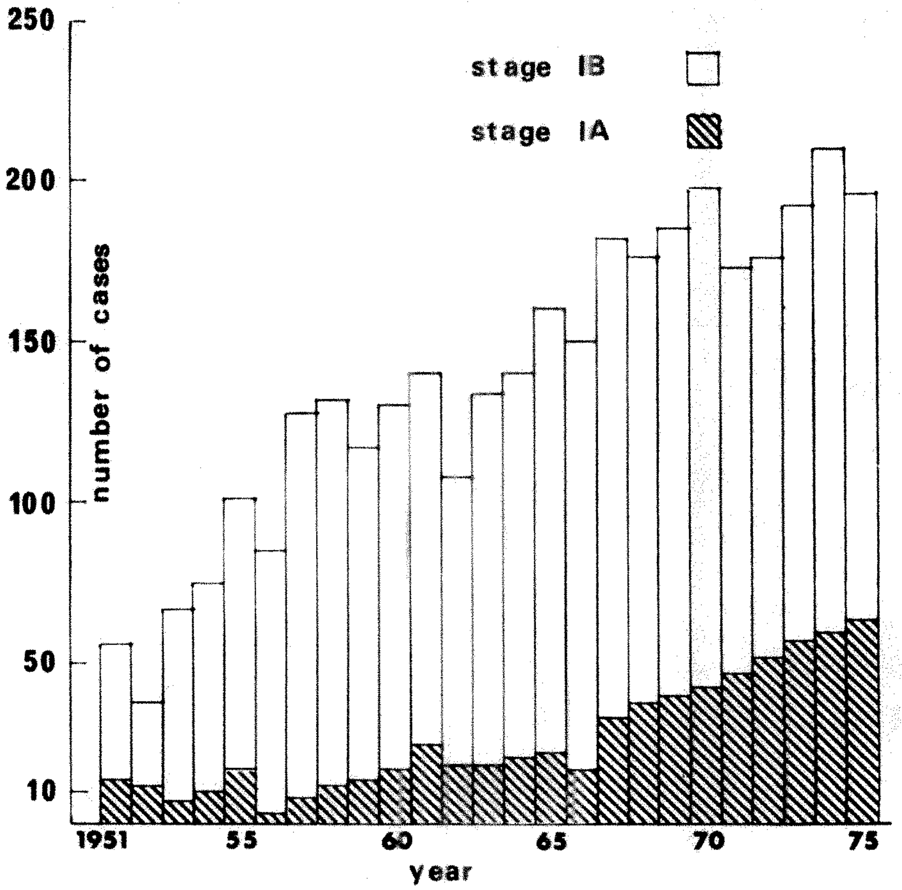

FIG. 1

The relative frequencies of Stage Ia and Ib carcinoma of the cervix treated in The Norwegian Radium Hospital during the years 1951 to 1975

Stage Ia and Ib carcinoma of the cervix among patients treated in The Norwegian Radium Hospital during the years 1951 to 1975.

In the 20-year period 1951–70, 367 patients with microinvasive carcinoma of the cervix (Stage Ia) were treated. Microinvasion was defined as tumour infiltration to a depth of no more than 5 mm. Occurrence of lymphatic or vascular invasion did not influence staging or choice of treatment. The present paper reports on 122 patients in whom the primary operation led to apparently complete removal of tumour tissue. The mean age of the patients was 44 years (range 24 to 77 years).

The diagnosis was made on conization specimens in 53 patients, on hysterectomy specimens in 65 patients and on large wedge biopsies in 4 patients.

The series was divided, according to the depth of stromal invasion, into four groups: (i) minimal stromal invasion, (ii) invasion of less than 1 mm; (iii) invasion of 1·0 to 2·9 mm, and (iv) invasion of 3 to 5 mm.

Invasion of blood vessels and lymphatic channels was found and considered 'certain' if the channel was lined by endothelium and 'possible' if the channel was not so lined.

The edges of operation specimens were carefully studied for the presence of tumour or carcinoma in situ.

Table I shows the manner in which the 122 patients were treated, while Table II gives

TABLE I

Treatment methods and recurrence

Treatment group	Total No.	Recurrence Vagina/cervix or bladder	Recurrence Pelvic wall
Conization	2	—	1
Hysterectomy	19	—	—
Extended hysterectomy	53	2	3
Conization + radium	34	1	—
Hysterectomy + radium	14	1	—
Total	122	4	4

TABLE II

Recurrence in relation to the treatment of the pelvic lymph nodes

Pelvic lymph nodes	Total No.	Recurrence Vagina/cervix or bladder	Recurrence Pelvic wall
Not treated	108	3	3
Removed	9	1	1
Irradiated	5	—	—
Total	122	4	4

information about the treatment of the pelvic lymph nodes and recurrence.

RESULTS

Histology

Three patients had adenocarcinomas, two had adenosquamous lesions, one patient had a microinvasive squamous cell carcinoma of the cervix with a concomitant endometrial adenocarcinoma and 116 patients had squamous cell carcinomas.

There were 42 patients who were classified as having carcinoma *in situ* with minimal stromal invasion. Stromal invasion with interlacing cords of neoplastic epithelium surrounded by moderate lymphocytic infiltration or a more marked inflammatory reaction was found in 80 patients.

Tumour cells in vascular channels were found in eight patients; five of these showed stromal invasion to a depth of less than 3 mm.

Tumour at the edge of resected tissue was found in one patient, and carcinoma *in situ* lesions in additional seven patients.

Follow-up

Details of follow-up are given in Table III. It should be noted that 5 of the 8 recurrences occurred after the conventional 5-year follow-up period. In one patient a pelvic lymph node metastasis was detected 13 years after primary treatment. The five-year crude survival rate in our series was 99 per cent.

The relation between depth of invasion, tumour in vasular channels and recurrences is shown in Table IV. Vascular channel invasion was commonest when tumours invaded more than 1 mm into the stroma.

Of the four patients with central recurrences two had carcinoma *in situ* at the edge of the tissue resected and one had tumour at this site; the fourth patient had tumour cells in lymphatic channels.

Of the four patients with pelvic wall recur-

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TABLE III

Recurrences and deaths in relation to time of follow-up

Duration of follow-up (years)	Total No. of patients	Total No. of recurrences		Died of cancer	Died of other causes
		Vagina/cervix or bladder	Pelvic wall		
Up to 5	122	2	1	1*	1
Up to 10	120	2	2	2	1
Up to 15	58	—	1	—	3
Up to 20	18	—	—	—	—
Up to 25	7	—	—	—	—

* died at 3½ years

TABLE IV

Correlation between depth of stromal infiltration, invasion in vessels and recurrence

Depth of infiltration (mm)	Total No.	Tumour in blood vessels or lymphatics		Recurrence	
		Certain	Possible	Vagina/cervix or bladder	Pelvic wall
'Minimal'	42	—	—	2	—
<1·0	25	1	1	1	1
1·0–2·9	27	4	1	1	1
3·0–5·0	28	3	4	—	2
Total	122	8	6	4	4
Per cent	100	6·5	5·0	3·3	3·3

TABLE V

Correlation between tumour involvement of vessels and recurrence

Involvement of blood vessels or lymphatics	Total No.	Recurrence	
		Vagina/cervix or bladder	Pelvic wall
None	108	2	1 (0·9 per cent)
Possible	6	—	—
Certain	8	2	3 (37·5 per cent)

rences, three had blood vessel invasion and none had carcinoma *in situ* or tumour at the edge of resected tissue. Of the 114 patients showing no clear evidence of blood vessels or lymphatics invasion, only one patient, with an adenocarcinoma of the cervix, developed a pelvic wall metastasis whereas 3 of 8 patients with tumour cells in blood vessels or lymphatics did so (Table V).

DISCUSSION

We agree that patients should only be classified as having Stage Ia carcinoma (or microinvasive carcinoma) of the cervix if the depth of stromal invasion is less than 5 mm, but we believe that blood vessel and lymphatic invasion or the presence or absence of neoplasia at the edge of a specimen should influence the method of treatment.

The accurate assessment of microinvasive carcinoma of the cervix requires systematic histological examination of an adequate specimen, and this is at least a cone biopsy containing the entire lesion. The depth of invasion should be measured by calibrated optical systems, and the search for lymphatic or blood vessel invasion should be meticulous.

If the specimen shows minimal stromal invasion without carcinoma *in situ* or tumour at the edge, further treatment is not necessary. If the depth of stromal invasion is less than 5 mm, the borders are free, and there is no tumour in lymphatic or blood vessels, total hysterectomy with conservation of the ovaries in younger patients is recommended. In older patients total hysterectomy and bilateral salpingo-oophorectomy, or intracavitary radium may be used.

If there is atypical epithelium at the edge of the resected tissue we believe that an extended hysterectomy (without lymph node dissection) is indicated unless there are contraindications to surgery in which case radiotherapy may be preferred.

When involvement of vascular spaces is found, we recommend Wertheim's hysterectomy or radiotherapy.

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THE EFFECTS OF MATERNALLY ADMINISTERED PETHIDINE OR EPIDURAL BUPIVACAINE ON THE FETUS AND NEWBORN

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Summary

The continuous fetal heart rate pattern, condition of the baby at birth and its subsequent behaviour were compared in three groups of infants whose mothers received during labour either no drugs, intramuscular pethidine or epidural bupivacaine. The blood levels of pethidine and bupivacaine were measured at delivery in a maternal vein, and umbilical artery and vein, and in the newborn during the first 48 hours of life. The only significant changes in the fetal heart rate pattern occurred in association with maternal hypotension or uterine hyperstimulation. The Apgar scores at one minutes were 7 or less in more infants in the intramuscular pethidine and epidural bupivacaine groups as compared with the controls. There were no differences in the Apgar scores at five minutes. Neonatal behaviour during the first six weeks of life was not significantly affected by pethidine or epidural bupivacaine when compared with the control group. Pethidine and bupivacaine were shown to cross the placenta freely. The half-life of these drugs in the newborn was longer than in the adult.

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CLIFFORD AND IRVING (1937) stated that 'The ultimate fate of the present methods of obstetric analgesia may well hinge on the price the infant must pay for the mother's comfort'. Although numerous studies have attempted to quantify this 'price', it is only in the last decade that the necessary technology to measure small quantities of drugs (Caldwell *et al*, 1978*a*) and systems to evaluate the newborn have been developed (Brazelton, 1973; Scanlon *et al*, 1974).

Previous studies (Aleksandrowicz and Aleksandrowicz, 1976; Richards and Bernal, 1972; Conway and Brackbill, 1970; Standley *et al*, 1974; Scanlon *et al*, 1974) have been open to criticism because of small sample size, the use of several analgesics or anaesthetics during labour, the selection of infants for study after birth, the failure to take into account social and obstetric variables and a failure to measure drug levels in the fetus and newborn.

The object of our prospective study was to assess the effects of maternal analgesia and also a large number of variables during pregnancy, labour and delivery on the condition of the baby at birth and its subsequent behaviour and development.

PATIENTS AND METHODS

Selection of patients

Married Caucasian women with no known medical, familial or obstetric disorders which could adversely affect the outcome of pregnancy were invited, during the second trimester of pregnancy, to participate in the study. They were allowed to select the method of analgesia since it was considered that random allocation to a drug group would have been both unethical and impractical. Of 145 patients, 35 elected not to have drugs during labour (control group), 51 requested intramuscular pethidine (pethidine group) and 59 requested epidural bupivacaine (epidural bupivacaine group). Eighteen other patients originally included in this study were excluded from the analysis as they had both pethidine and bupivacaine during labour, or were delivered by Caesarean section.

There were no differences between the three groups with respect to maternal age, social class, height, weight at booking, weight gained during pregnancy, gestational age at booking and delivery, incidence of smoking and antenatal complications, birth weight and sex of the infant, and weight of the placenta (Tables I and II). There were no instances of premature labour or breech delivery.

Obstetric management and analgesia

After initial selection, patients received routine antenatal care and were prescribed only iron and folic acid. At the onset of labour continuous fetal heart rate monitoring was undertaken in all patients and uterine contractions were recorded with either an external tocograph or an intrauterine catheter in the oxytocin-induced and augmented labours (Steer, 1977). Patients in the pethidine group received intramuscular injections of 100 or 150 mg of pethidine with 10 mg of metaclopromide whenever they requested pain relief. Women given epidural analgesia had an epidural catheter inserted through a Touhy needle in the epidural space; the catheter was passed 3 cm cranially from the tip of the needle and a local anaesthetic solution of 10 to 14 ml of 0·375 per cent bupivacaine was injected over 10 minutes with the patient in the left lateral position. An intravenous infusion of 5 per cent dextrose in water was commenced before the epidural injection. The maternal blood pressure was recorded before the injection of bupivacaine and then at 5 minute intervals for the first 30 minutes and at 15 minute intervals thereafter. A number of women in each group used Entonox (nitrous oxide/oxygen) inhalation shortly before delivery. In 25 of the 145 patients labour was induced (Table III).

The administration of oxygen by face mask to the infant or intermittent positive pressure ventilation were determined by the clinical condition of the baby at birth.

The Apgar score was recorded at one and five minutes after delivery.

Pharmacological measurement

At delivery, 5 ml of blood was collected from a maternal forearm vein and the umbilical vein and artery, and the pH was measured. Capillary blood was collected from the heel of the newborn infant at 2, 6, 12, 24 and 48 hours after birth. All blood samples were stored at 0°C. The concentrations of pethidine and bupivacaine in maternal and umbilical cord blood were assayed by gas-liquid chromatography (GLC) and in neonatal blood by gas liquid chromatography-mass spectrometry (GLC–MS) according to Caldwell *et al* (1976 and 1978*a* and *b*). The rate of elimination of the drugs from the newborn was estimated by calculation of their half life (Caldwell *et al*, 1978*a*).

Behavioural assessment

At 36 weeks gestation patients were asked to complete a set of self-administered psychological questionnaires designed to assess their mood, symptoms of pregnancy and expectations of the labour and of their infant.

The behaviour of the infants was assessed by a variety of procedures from delivery until six weeks of age. To preclude knowledge of the preceding events, the psychologist was admitted to the labour suite only when the head of the fetus was crowning. The following behaviours were recorded at 15 second intervals for the first 20 minutes after birth: the infant's spontaneous behaviour (movement, visual, auditory responses and state of alertness), medical procedures (weighing, examination, resuscitation), and the mother's interaction with her infant (holding, talking, suckling). At the end of this period a formal assessment of the infant's ability was made, using selected items from the Brazelton Neonatal Behavioural Assessment Scale (Brazelton, 1973). The infants were re-examined at about 24 hours after delivery and on days 3, 7, 21 and 42 using the full Brazelton scale. The assessment contains 23 items scored on a 9 point scale which characterize four areas of neonatal behaviour: (i) attention and orientation to the environment; (ii) muscle tone and the motor organization; (iii) control and organization of states of sleep and wakefulness; and (iv) the physiological response to stressful stimuli. Most items score the infant's best performance.

The test was performed midway between feeds and took approximately 30 minutes to complete. In addition to the behavioural assessment, an independent neurological examination of each infant was made by a paediatrician using the Prechtl Neurological Examination (Prechtl and Beintema, 1964).

All observations and assessments were made without knowledge of the maternal medication, and schedules were arranged to avoid consecutive assessment by the same psychologist. Agreement between assessments made by the four psychologists remained above 87 per cent.

Statistical analysis

Multiple regression with the behavioural measures as the dependent variables was used throughout. The independent variables were the drug used, parity, social class, maximum rate of administration of oxytocin, length of first and second stages of labour, method of delivery, method of resuscitation at delivery, Apgar scores at one and five minutes, and 13 scores obtained from the maternal mood questionnaire recorded antenatally.

Categorical variables such as drug group and method of delivery, which could not be directly entered into the regression equation, were each represented by a set of dummy variables. These are created by setting up a new variable for each class of categorical variable, and assigning scores of 1 or 0 on these dummy variables to all cases, depending upon their presence or absence in each of the categories. One category is always excluded because it is represented by zeros on all the other categories, and thus becomes a reference category by which the effects of the other dummies may be judged and interpreted. As an example, two dummy variables were created to represent the three drug groups. A baby whose mother had received pethidine was given a score of 1 on the first variable and 0 on the second, a baby in the epidural bupivacaine group was assigned scores of 0 on the first and 1 on the second variable, while a baby whose mother had received no drugs was given scores of 0 on both variables.

The multiple regression technique permits the evaluation of the importance of any particular independent variable by controlling for the confounding influence of the other independent variables. The analysis was carried out in two steps. On the first step, only the dummy variables representing the drug groups were included as independent variables, while on the second step maternal, labour and delivery variables were inserted into the equation. By comparing the results of the first and second analysis, it could be seen whether apparently significant differences in behaviour between the drug groups were in fact due to differences in labour and delivery variables, or, alternatively, whether significant differences between the drug groups were being masked by the confounding effects of these other variables.

RESULTS

The duration of the first and second stages of labour and the amount of blood loss at delivery were significantly greater in the pethidine and epidural bupivacaine groups (Table I). Table II shows that the proportion of primipara as compared with multipara was significantly greater in the pethidine and epidural bupivacaine groups than in the control group. The incidence of oxytocin-induced and augmented labours and forceps deliveries was also significantly greater in the drug groups (Table II) although there was no difference in the indications for induction between the two drug groups (Table III). There was no difference in the duration of the third stage (Table I) or the presence of meconium-stained amniotic fluid in the three groups (Table II).

Fetal heart rate patterns during labour

Changes in the fetal heart rate pattern after administration of either pethidine or epidural bupivacaine were analysed in two ways. The first method was to simply note the presence of late decelerations on the trace, and the second was to derive an acceleration or deceleration index as follows:

$$\frac{\text{number of accelerations or decelerations} \times 100}{\text{number of contractions in a 30-minute period}}$$

The index was assessed in the 30 minutes before the first drug administration and in the two subsequent 30 minute periods. There were no significant differences in these indices between the pethidine and epidural bupivacaine groups. Late decelerations occurred in eight patients following the use of epidural bupivacaine. In five of these patients, maternal hypotension was present (blood pressure below 90/60 mm Hg) and uterine hyperstimulation (contractions occurring more than once every 3 minutes) caused by oxytocin was evident in three. In this study uterine hyperstimulation or maternal hypotension was always followed by late decelerations.

TABLE I

Maternal and obstetric variables

Variables	No drug (n = 35) Mean±SD	Pethidine (n = 51) Mean±SD	Epirudal bupivacaine (n = 59) Mean±SD	Significance of difference between groups*
Maternal age (years)	26·9± 3·6	27·3± 5·4	28·2± 4·3	NS
Maternal height (cm)	162·2± 5·9	161·2± 5·4	160·8± 6·2	NS
Weight at booking (kg)	57·1± 5·7	58·3± 6·5	59·9± 8·8	NS
Weight gain (kg)	12·3± 9·8	11·1± 4·2	10·1± 3·9	NS
Gestational age at booking by dates (weeks)	13·9± 3·8	13·6± 4·9	15·4± 6·4	NS
Gestational age at booking by fundal height (weeks)	15·2± 5·6	14·1± 4·6	15±7 6·7	NS
Gestational age at labour (weeks)	40·2± 1·0	40·0± 1·1	40·3± 0·9	NS
Maximum dose of oxytocin (mU/minute)	0·0± 0·0	11·1± 4·7	9·9± 8·2	NS†
Duration 1st stage (minutes)	345·2±171·4	471·2±222·7	511·7±247·1	p <0·005
Duration 2nd stage (minutes)	25·9± 18·2	37·5± 31·9	67·1± 42·3	p <0·001
Duration 3rd stage (minutes)	5·3± 2·3	5·7± 2·6	5·3± 1·9	NS
Blood loss (ml)	179·4± 78·1	219·8± 91·3	249·1± 94·1	p <0·005
Placental weight (g)	630·1±121·1	645·3±111·2	607·0±147·5	NS
Infant weight (kg)	3·5± 0·4	3·5± 0·4	3·5± 0·4	NS

* From analysis of variance

† From t-test between pethidine and bupivacaine groups

NS = not significant

TABLE II

Maternal and obstetric factors

Factor	No drug (n = 35)		Pethidine (n = 51)		Epidural bupivacaine (n = 59)		Total (n = 145)	
	No.	Per cent	No.	Per cent	No.	Per cent	No.	Per cent
*Parity**								
Primipara	14	40·0	32	62·7	41	69·5	87	60·0
Multipara	21	60·0	19	37·3	18	30·5	58	40·0
Social class								
I/II	16	45·7	22	43·1	37	62·7	75	51·7
III	11	31·4	24	47·1	15	25·4	50	34·5
IV/V	5	14·3	4	7·8	7	11·9	16	11·0
Not known	3	8·6	1	2·0	0	0·0	4	2·8
Smoking habit								
Smoker	8	22·9	16	31·4	17	28·8	41	28·3
Non-smoker	27	77·1	35	68·6	42	71·2	104	71·7
Antenatal complications								
None	27	77·1	41	80·4	41	69·5	109	75·2
Pre-eclampsia	3	8·6	3	5·9	8	13·6	14	9·7
Urinary infection	2	5·7	2	3·9	3	5·1	7	4·8
Antepartum haemorrhage	0	0·0	2	3·9	1	1·7	3	2·1
Threatened abortion	1	2·9	2	3·9	2	3·4	5	3·4
Anaemia	2	5·7	0	0·0	2	3·4	4	2·1
Other	0	0·0	1	2·0	2	3·4	3	2·1
Use of oxytocin†								
None	35	100·0	40	78·4	26	44·1	101	69·7
To augment contractions	0	0·0	5	9·8	14	23·7	19	13·1
To induce labour	0	0·0	6	11·8	19	32·2	25	17·2
Amniotic fluid								
Clear	34	97·1	48	94·1	54	91·5	136	93·8
Meconium-stained	1	2·9	3	5·9	5	8·5	9	6·2
Forceps‡								
Not used	33	94·3	46	90·2	32	54·2	111	76·6
Used	2	5·7	5	9·8	27	45·8	34	23·4
Infant sex								
Male	15	42·9	27	52·9	28	47·5	70	48·3
Female	20	57·1	24	47·1	31	52·5	75	51·7

* $\chi^2 = 8{\cdot}21$, 2 df, $p < 0{\cdot}02$

† $\chi^2 = 35{\cdot}41$, 4 df, $p < 0{\cdot}001$

‡ $\chi^2 = 27{\cdot}79$, 2 df, $p < 0{\cdot}001$

TABLE III

Indications for induction of labour

Indications for induction	No drug	Pethidine	Epidural bupivacaine	Totals
Spontaneous onset of labour	35	45	40	120
Raised blood pressure at term without proteinuria	0	1	2	3
Maternal weight loss and proteinuria	0	0	1	1
Gestational age greater than 290 days	0	2	12	14
Patient request	0	3	4	7
Totals	35	51	59	145

TABLE IV

Infant status at birth

	Resuscitation			
Apgar score at 1 minute	Suction	Oxygen by face mask	Intermittent positive pressure respiration	Total
No drug				
≦7	0	0	0	0
8	2	0	0	2
9	27	0	0	27
10	6	0	0	6
Total	35	0	0	35
Pethidine				
≦7	2	5	3	10
8	9	6	0	15
9	20	1	0	21
10	5	0	0	5
Total	36	12	3	51
Epidural bupivacaine				
≦7	0	0	2	2
8	15	4	0	19
9	30	2	0	32
10	6	0	0	6
Total	51	6	2	59

Status of the newborn infant

Table IV shows that in addition to routine mucus extraction, 12 of the 51 infants in the pethidine group and six of the 59 in the epidural bupivacaine group were given oxygen by face mask. No babies in the control group required resuscitation. Three infants in the pethidine and two in the epidural bupivacaine groups required intermittent positive pressure respiration ($p < 0{\cdot}001$). Ten infants in the pethidine group had a one-minute Apgar score of 7 or less as compared with none in the control group ($p < 0{\cdot}001$). There were no significant difference in the five-minute Apgar scores between the three groups.

Drug levels

The mean total dose and number of injections of pethidine and epidural bupivacaine are shown in Figures 1 and 2.

The concentrations of pethidine and bupivacaine in the maternal and umbilical cord blood at delivery are shown in Table V. The concentrations of both drugs in neonatal blood fell monoexponentially with time over the first

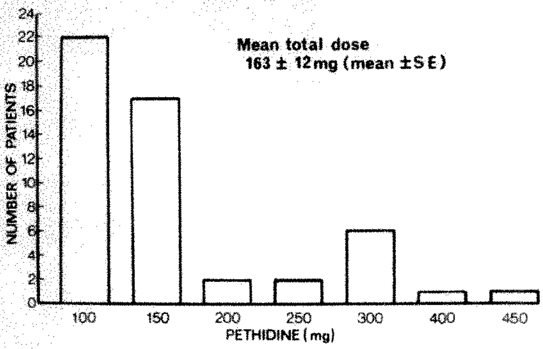

FIG. 1
Distribution of total dosages of pethidine.

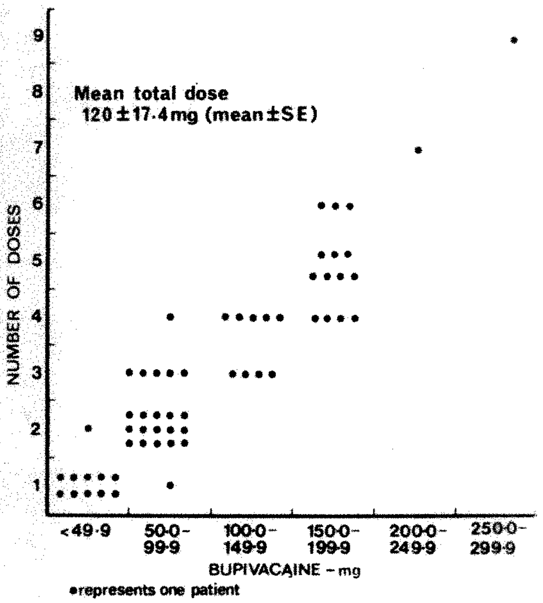

FIG. 2
Distribution of total dosages of epidural bupivacaine.

48 hours of life, and half-lives calculated from log blood concentration-time curves for each infant are listed in Table V.

TABLE V
Concentration of pethidine and bupivacaine in mother and infant at birth

	Pethidine (ng/ml) (n = 39)*	Bupivacaine (ng/ml) (n = 53)†
	Mean ± SD	Mean ± SD
Maternal vein (Mv)	256·3 ± 23·4	231·2 ± 14
Umbilical vein (Uv)	213·2 ± 18·5	80·5 ± 6·6
Umbilical artery (Ua)	222·0 ± 22·4	79·3 ± 6·8
Mv/Uv ratio	0·83	0·35
Mv/Ua ratio	0·98	0·31
Neonatal elimination $t_{1/2}$ half-life (hours)	22·4 ± 4·7	14 ± 1·1

* No blood samples 12 patients
† No blood samples 6 patients

Behavioural effects on the infant

There were few differences between groups in behaviour of the mothers and infants in the delivery room. Mothers in the epidural group spent less time talking to the infant than the control group ($p < 0{\cdot}01$) and the infants in the bupivacaine group were less responsive to the human voice ($p < 0{\cdot}05$; Table VI). There were no significant differences in the level of social responsiveness, motor organization and state control in the three groups.

Subsequent Brazelton assessments failed to reveal any significant difference (between the three groups) in the behaviour of the infants on day 1, 7, 21 and 42 of life. The ability of the infants to ignore the repeated ringing of a bell (habituation response) was impaired on day 3 in the pethidine group ($p < 0{\cdot}05$) compared with the control group. There were no significant differences in the results of the Prechtl Neonatal Assessment between the three groups.

DISCUSSION

The design of the study and the method of statistical analysis allowed us to distinguish the effect of drugs from the combined influence of drugs plus obstetric factors such as parity, oxytocin stimulation, the length of labour and the mode of delivery.

Pethidine did not affect the fetal heart rate, but late decelerations in the fetal heart rate pattern were seen in 8 of the 59 patients who had epidural bupivacaine and were secondary to either maternal hypotension or uterine hyperstimulation. These findings are in agreement with those of Noble *et al* (1971), Schifrin (1972) and Wingate *et al* (1974). They confirm the view

TABLE VI

Measures of neonatal behaviour differing between the groups

	No drug (n = 35) Mean ± SD	Pethidine (n = 51) Mean ± SD	Epidural bupivacaine (n = 59) Mean ± SD
Duration that mother talks to baby at delivery (minutes)	12·84±22·12	5·66±8·56	4·73±8·51
Animate auditory score at delivery (Brazelton score)	6·07± 1·4	5·42±1·86	4·74±1·94
Habituation to a bell on day three (Brazelton score)	7·42± 1·4	6·00±2·00	7·76±1·55

that the major cause of the fetal heart rate abnormalities is probably secondary to decreased perfusion of the intervillous space rather than to a direct quinidine like effect of the bupivacaine on the fetal myocardium.

Significantly more of the babies born to mothers given pethidine had an Apgar score of 7 or less at one minute, and required oxygen by face mask or intermittent positive pressure respiration. It is well known that pethidine acts as a respiratory depressant, but the effect was transitory as shown by the absence of any significant difference between groups in the five-minute Apgar score and the subsequent behaviour of the infants. Measurement of the bupivacaine and pethidine concentrations in maternal and umbilical cord blood at delivery showed that both drugs freely cross the placenta. The mean maternal vein/umbilical vein concentration ratios were 0·35 for bupivacaine and 0·83 for pethidine, both values corresponding very closely to those obtained by other workers (Morrison *et al*, 1973; Reynolds and Taylor, 1970).

The blood elimination half-lives of pethidine and bupivacaine from the newborn were 22·7 hours and 14 hours respectively and were considerably longer than those quoted for the adult, namely 3·2 hours for pethidine (Mather *et al*, 1975) and 1·25 hours for bupivacaine (Caldwell *et al*, 1976). The difference is probably due to impaired metabolism in the newborn (Caldwell *et al*, 1978*c*).

The minimal adverse 'drug' effect on neonatal behaviour during the first six weeks of life as judged by the Brazelton score is consistent with the recent findings of Scanlon *et al* (1976) and Tronick *et al* (1976). However, it must be stressed that the conclusions only apply to healthy women with uncomplicated pregnancies and deliveries and normal infants. The doses of drugs used were relatively small and it is not possible to say what the adverse effects might be on the compromised fetus. Furthermore, this between group analysis took account only of the presence or absence of each drug. It therefore does not permit analysis of the variation within each group due to differences in drug exposure. Considerable differences in neonatal behaviour were discernible within each drug group in relation to the concentrations of pethidine and bupivacaine in umbilical cord blood and the infant's ability to metabolize the drugs. The significance of these findings and the influence of other obstetric variables on neonatal behaviour will be discussed in subsequent papers.

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FETAL BREATHING MOVEMENTS AND FETAL DISTRESS

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Summary

Twenty-seven pregnancies were monitored by antenatal cardiotocographs, daily fetal movement counts and an assessment of fetal breathing activity by real time scanning, and the results of these tests were related to the development of fetal distress during the first stage of labour. The proportion of time during which fetal breathing movements were present, determined over only a short period of time, was found to be a useful predictor of fetal behaviour during labour.

BREATHING movements occur in the human fetus from early pregnancy, and have been studied extensively by ultrasonic A scan (Boddy and Dawes, 1975). The recent development of real time scanning which displays a moving composite picture is ideally suited to investigation of these movements (Fox and Hohler, 1977, Roberts *et al*, 1977) and is now the method most frequently used. Boddy and Dawes (1975) and Manning (1977), have suggested that the fetus which is destined to develop fetal distress during labour will show reduced fetal breathing movements (FBMs), but the picture is complicated by diurnal variation (Fox and Hohler, 1977, Roberts *et al* 1977), maternal activity and blood glucose levels (Fox and Hohler, 1977), smoking (Manning and Feyerabend, 1976), uterine activity (Manning, 1977) and drug administration (Boddy and Dawes, 1975).

Maternal assessment of fetal movements is often used as a simple outpatient indicator of fetal wellbeing, and both Pearson and Weaver (1976) and Sadovsky and Yaffe (1973) have suggested that a decline in the daily fetal movement count (DFMC) to under 10/12 hours is a warning that the fetus might be in jeopardy. Assessment of fetal wellbeing can also be made by external cardiotocography and this can readily be applied to those patients who report a decrease in fetal movements.

This study was undertaken to determine whether fetal breathing activity as assessed by real time scanning could be used as an index of fetal well-being, particularly behaviour during labour, and to augment assessment by daily fetal movement counts and external cardiotocography.

PATIENTS AND METHODS

The analysis is based on a total of 81 observation periods in 27 patients, giving an average of 3·0 scans per patient (range 1 to 8). Outpatients were studied once weekly, and inpatients two or three times each week. The majority of studies were performed in the early evening to reduce the effect of diurnal variation (Roberts *et al*, 1977). Indications for inclusion in the study were essential hypertension (3 patients), pre-eclampsia (9 patients), a clinical impression of intrauterine growth retardation (12 patients), weight loss (5 patients), reduced fetal movement (7 patients), antepartum haemorrhage (2 patients) or prolonged pregnancy (2 patients). Some patients were included for more than one indication.

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Each patient kept a daily record of fetal movement using a Cardiff 'Count to Ten Chart', and had an antenatal cardiotocograph (CTG) and biparietal diameter (BPD) estimation performed on the same day as the FBM count. Cardiotocographs were scored by the 'six point score' (Pearson and Weaver, 1978).

FBM assessment and CTGs were made with the patient in the supine position with a 15° lateral tilt to reduce caval compression.

Scans were performed using an Ekolife real time scanner (Smith Kline) and a 3·5 MHz transducer. Abdominal palpation was performed first followed by a BPD measurement. To measure the FBM, either a longitudinal section of the fetal trunk or a transverse section showing the heart valve movement was obtained, and fetal breathing was considered to be occurring when there was rhythmical contraction and expansion of the chest wall. In the longitudinal section, this was accompanied by paradoxical movement of the abdominal wall.

The total time during which these chest movements were seen was recorded with a stopwatch and expressed as a percentage of the total observation time (the FBM percentage). The stopwatch was stopped two seconds after the end of a breath if another breath had not started. Each observation period lasted for 15 minutes, except that if neither fetal body or limb movements nor fetal chest movements were seen in the first 15 minutes, observation was continued for a second 15 minute period because the uncompromised fetus is sometimes apnoeic for up to 30 minutes (Roberts *et al*, 1977). Time when the view was obscured by gross fetal movements was discounted.

Fetal heart rates were monitored continuously during labour, and for the purposes of this study fetal distress was defined as the occurrence of late decelerations. The statistical analysis was by the Mann-Whitney test.

RESULTS

All 27 patients in the study were delivered between 37 and 42 weeks gestational age; 19 achieved spontaneous vaginal delivery, and 4 were delivered by low forceps. Three of the forceps deliveries were for delay and one was for a fetal bradycardia in the second stage attributed to a tight loop of cord around the baby's neck. All these 23 babies had Apgar scores of 7 or over at one minute, and all except one were between the relevant 10th and 90th centiles for birth weight (Tanner and Thomson, 1970).

The remaining four developed fetal distress during the first stage of labour. Three patients were delivered by emergency Caesarean Section of 'light-for-dates' infants with respective Apgar scores at one minute of 4, 7 and 8. The fourth patient was delivered by mid-cavity forceps through an incompletely dilated cervix of a baby of appropriate weight and an Apgar score of 8 at one minute.

Patterns of fetal breathing movements

The most common pattern of FBM observed was of rapid (around 60/minute) small amplitude

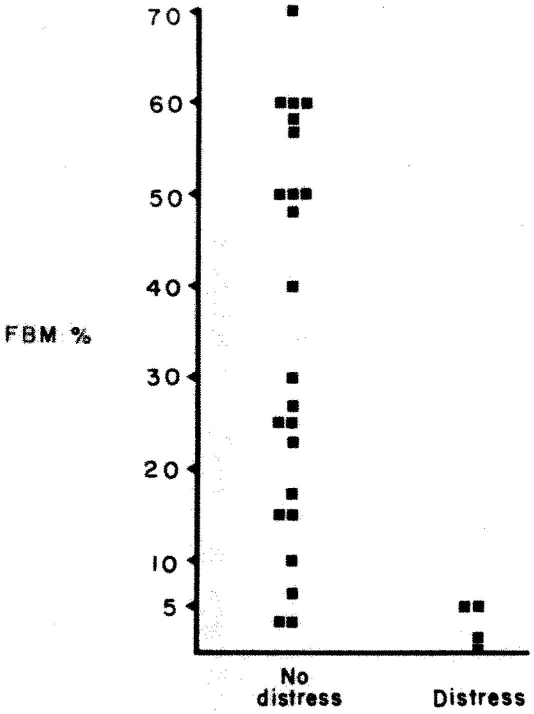

FIG. 1

The distribution of FBM percentage counts in the fetal 'distress' and 'no fetal distress' groups. Distribution of FBM percentages (time during which fetal breathing movements are present as a percentage of observation time) in the 'fetal distress' and 'no fetal distress' groups.

TABLE I

Details of the 10 patients with abnormal results

Patient No.	Smoker	Last DFMC	Last CTG score*	Last FBM percentage†	Fetal distress	Appropriate weight or light-for-dates
1	Yes	8	5	57	No	Appropriate
2	No	9	5	50	No	Appropriate
3	Yes	5	5	48	No	Appropriate
4	Yes	0	5	60	No	Appropriate
5	Yes	0	4	0	Yes	Appropriate
6	No	>20	4	1	Yes	L.F.D.
7	No	>20	4	5	Yes	L.F.D.
8	Yes	>20	4	3	No	Appropriate
9	Yes	>20	5	5	Yes	L.F.D.
10	Yes	8	5	3	No	L.F.D.

* Pearson and Weaver (1978)

† Time during which FBMs were present expressed as a percentage of total observation time.

DFMC = daily fetal movement count
CTG = cardiotocograph
FBM = fetal breathing movement

movements progressively increasing in amplitude and then decreasing. Fetal body movement preceded or followed this pattern, but did not usually coincide. In one patient isolated rapid large amplitude movements were seen and these were thought to be the hiccoughs described by Lewis and Trudinger (1977).

In several patients very few FBMs were seen at the start of an observation period, but activity increased towards the end, and in one patient neither FBMs nor body movements were seen in the first 15 minutes although in the next 15 minutes the fetus became normally active and a normal FBM percentage was recorded. In the one other patient where observation was continued for a second 15 minute period, no FBMs were noted over the whole 30 minutes.

Fetal breathing movements and fetal distress

When the last recorded FBM percentage (2 to 5 days before delivery) is compared with the outcome, the group who developed no distress in the first stage had a mean FBM percentage of 34·7 (range 3 to 70). The patients who did develop fetal distress in the first stage had a mean FBM percentage of 2·75 (range 0 to 5). FBM percentages are shown in Figure 1 and the difference between the two groups is statistically significant ($u = 4$, $p < 0 \cdot 005$). In one of the four patients who did develop distress, low FBM percentages were first noted three weeks before delivery.

TABLE II

Reliability of the three tests

	Correct	False positive	False negative
FBM	8	2	0
CTG	8	1	1
DFMC	2	5	3

CTG = cardiotocograph
DFMC = daily fetal movement count
FBM = fetal breathing movement

In 12 patients the FBM percentage was measured on three or more occasions and in most patients it decreased towards term, but remained above 5. In only three patients did the FBM percentage fall from above 5 to below 5, and in two of these fetal distresss subsequently developed.

The comparative reliability of FBM percentages, DFMCs and cardiotocography

In 17 of the patients all the tests gave normal results and the outcome was labour with no fetal distress and a baby of appropriate weight. The details of the other 10 patients are shown in Table I.

By considering abnormal results as positive (i.e. DFMC below 10, CTG score 4 or below and FBM percentage 5 or below), the incidence of correct, false positive and false negative results for each test is shown in Table II.

Smoking

There were 7 cigarette smokers amongst the 27 patients whose results were analysed and all 7 appear in Table I. The two patients whose FBM percentages gave false positive results both smoked over ten cigarettes a day.

DISCUSSION

Fetal breathing studies have not yet found a place in routine clinical practice and this study attempts to evaluate fetal breathing activity in a way which could be applied to an out patient population. The method employed was simple and required only a real time scanner and a stopwatch. No specific glucose load was used (Trudinger *et al*, 1978), but measurements were made at the peak of expected diurnal variation (Roberts *et al*, 1977). The observation period was deliberately short and the practice of extending it in the absence of movement is analagous to that of repeating an abnormal result before acting upon it. Unfortunately, this practice presupposes that breathing is the normal situation and apnoea is abnormal. A delay of only 2 seconds was used before recording apnoea, in contrast to the usual 6 second delay, as this was found to be easier when using a stopwatch. In most patients an increase in FBMs was seen during the observation period and this might reflect a response of the fetus to the stimulus of ultrasound.

Previous suggestions (Boddy and Dawes, 1975; Manning, 1977) that FBMs are reduced in the compromised fetus were confirmed, and an FBM percentage of over 5 successfully predicted normal fetal behaviour in labour in 20 out of 21 patients. The one exception required a low forceps delivery for a bradycardia in the second stage which was attributed to a tight loop of cord around the baby's neck. In the 6 patients with a low FBM percentage, fetal distress developed in 4 and the other 2 were heavy smokers. Smoking is known to depress fetal breathing and this result shows that any low FBM percentage in a patient who smokes must be interpreted with caution.

Daily fetal movement counting is possible for all patients but is highly subjective. It is intended as a screening test to detect the fetus at risk of dying *in utero* rather than as a predictor of behaviour in labour and in this sense it is perhaps unfair to compare daily fetal movement counts with cardiotocography and the proportion of time during which fetal breathing occurred in Table II. The five false positive low DFMCs demonstrate the importance of careful evaluation of a patient who reports low movements. The three patients whose DFMCs were falsely negative all had low FBM percentages and all produced light-for-dates babies. These patients had all been included in the study because of the clinical impression of intrauterine growth retardation and it seems that FBM percentages offer a valuable additional way of assessing fetal wellbeing in this group where maternal assessment of fetal activity may be misleading.

Biochemical tests of fetal wellbeing have been used for many years, but reflect, at best, the situation when the specimen was collected. FBM assessment provides up to date information which can be added to that obtained from cardiotocography. The cardiotocograph score will differentiate between a non-compromised fetus and one which is best delivered by urgent Caesarean section (Pearson and Weaver, 1978), and in addition the FBM percentage will give some indication of placental reserve and whether the fetus is likely to become distressed during labour. In this study four patients, whose CTGs scores were 4, all had abnormally low FBM percentages, but no CTG score was below 4 and no fetus showed the gasps or almost continuous breathing described by Trudinger *et al* (1978). A further study to compare breathing patterns and CTG scores in the seriously compromised fetus would be valuable.

This study has shown that useful assessment of fetal breathing movements can be obtained over a short observation period on outpatients, and there is need for a larger scale study of this application.

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FETAL BREATHING AND GENERALIZED FETAL MOVEMENTS IN NORMAL ANTENATAL PATIENTS

BY

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Summary

Fetal breathing movements (FBM) and generalized fetal movements (GFM) were recorded for 30 minutes using a real time B-scan instrument in 46 women with uncomplicated pregnancies. FBM occurred for $27 \cdot 6 \pm 3 \cdot 5$ (SE) per cent and GFM for $10 \cdot 9 \pm 0 \cdot 9$ (SE) per cent of the recording time. The time occupied by FBM was not significantly related to smoking, meal times or plasma glucose concentrations. FBM were absent during the observation period in 15 per cent of patients and present for less than 10 per cent of the time in 33 per cent of patients.

THE recording of human fetal breathing movements (FBM) using the A-mode ultrasonic scanning system requires some expertise and its interpretation is often unsatisfactory (Farman *et al*, 1975). Although recent improvements in real time scanners have made the identification of FBM easier there would appear to be a significant disparity in its incidence as assessed by the two methods (Boddy and Dawes, 1974; Marsal, 1977) even when factors known to influence FBM such as maternal exercise, abdominal palpation, the time of day and food or drug intake (Boddy *et al*, 1974) are taken into account. A study of FBM in a series of normal pregnant women attending the antenatal clinic was therefore undertaken using the real time ultrasound method.

METHOD

Forty-six women with normal singleton pregnancies between 31 and 37 weeks gestation were studied. All were subsequently delivered of normal infants of appropriate weight for gestational age with an Apgar score of 8 or more at 5 minutes. There were 16 primigravidae, 22 women were in their second pregnancy, 6 were in their third and 2 in their fourth pregnancy. Their mean age was 25 years (range 17 to 33 years). Each patient was examined on one occasion for approximately 30 minutes using a linear array real time B-scan instrument (ADR Model 2130) with a 3·5 MHz transducer. The observations were made on the semi-recumbent patients before the routine antenatal examination and after approximately five minutes rest. No restriction had been placed upon smoking or dietary habits and all the observations were made in the morning except for two patients who were examined in the early afternoon. None of the mothers was taking drugs other than haematinics.

A longitudinal scan through the fetal chest and abdomen was obtained; a breathing movement was recorded when the anterior chest wall and abdomen moved in opposite directions associated with an increase in the curvature of the fetal spine. These movements were recorded using a foot switch which controlled an event marker on a two-channel chart recorder (Devices Model 2M). Generalized fetal movements (GFM), defined as movements of the fetal trunk, were recorded on the second channel of the chart recorder the foot switch being depressed for the total period during which movements of the fetal trunk occurred. Because of the difficulty in recognizing FBM when GFM were occurring, breathing movements during these periods of general fetal activity were ignored. Absence of FBM for longer than 6 seconds was defined as non-breathing or apnoea. The time occupied by FBM and GFM are expressed as mean percentages of the total recording time with standard errors.

RESULTS

The mean time occupied by FBM was 27·6±3·5 (SE) per cent of the recording time in 45 patients. One patient was excluded from this calculation because only fetal hiccups were observed. This type of chest wall movement was not unlike a breathing movement in that each part of the fetal anatomy moved in a similar direction but the movement itself was considerably more rapid and was vigorous and jerking in character. The mean time occupied by GFM in this study was 10·9±0·9 (SE) per cent of recording time.

The time interval between the patient's last meal and the examination was recorded on 43 occasions and there was no correlation between this interval and the percentage time spent in FBM or GFM. Using the Spearman Rank correlation method of non-parametric analysis no correlation ($r = -0{\cdot}16$) could be established between FBM and GFM and the plasma glucose concentration estimated in a venous blood sample (mean 5·2±0·1 (SE) mmol/l; range 4·2 to 7·2 mmol/l) taken at the end of the recording period.

The smoking habit of each patient was recorded; 32 were non-smokers and 14 were smokers. The number of cigarettes smoked ranged between 5 and 30 per day with a mean of 17. The interval between smoking and recording was noted in 12 patients and the mean was 99±11 (SE) minutes (range 40 to 165 minutes). No significant difference in the mean duration time occupied by FBM could be demonstrated between the smokers 22·5±5·0 (SE) per cent and the non-smokers (29·9±4·6 (SE) per cent) using the Mann-Whitney U test. Also there was no correlation between the time-occupied by FBM and the time interval between the last cigarette and the recording.

DISCUSSION

The mean times occupied by FBM and GFM in this study (27·2 and 11·5 per cent) were comparable with the results of Patrick (1977) whose respective figures were 31·8 and 8·2 per cent. In both, the time occupied by FBM was lower than previously reported by Boddy and Dawes (1974), Marsal (1977) and Manning *et al* (1975) using the A-mode technique, possibly because episodes of FBM occurring during the GFM were excluded and because the real time method avoids some of the artifact inherent in A-mode recordings (Farman *et al*, 1975; Marsal, 1977).

It is of note that on one occasion fetal hiccups were observed which were not associated with normal FBM. Activity suggestive of fetal gasping movements has been described elsewhere (Boddy and Dawes, 1974) but was not seen in this series.

The wide range in time occupied by FBM in apparently normal pregnancies suggests that this type of information about the fetus will not be clinically useful unless recorded under carefully controlled circumstances. It would appear that although the presence of FBM may indicate a normal fetal state, the absence of such movements (7 patients) or their occurrence for less than 10 per cent of the recording time (15 patients) does not necessarily indicate abnormality; further study is required. Furthermore the absence of FBM for intervals exceeding five minutes was noted in 26 recordings in this series although this is said to be an unusual finding after 32 weeks gestation (K. Boddy, 1977, personal communication). In contrast to previous reports, FBM did not correlate with maternal smoking, meal times or plasma glucose concentration (Boddy and Dawes, 1974; Patrick, 1977; Manning *et al*, 1975). The mean time interval between smoking and recording in this series was over 90 minutes by which time the effect of smoking is probably almost abolished (Manning *et al*, 1975). The failure to establish a relationship between FBM and plasma glucose may perhaps be explained by the observation that the maximal increase in the time occupied by FBM in response to maternal glucose ingestion has a lag time of at least one hour (Lewis *et al*, 1978).

It may be that study of the rate and depth of fetal breathing will give more information about the state of the fetus. However, more sophisticated recording methods would be needed to study there aspects of fetal breathing.

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MATURITY OF FETAL LUNGS TESTED BY PRODUCTION OF STABLE MICROBUBBLES IN AMNIOTIC FLUID

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Summary

Lung surfactant in amniotic fluid, and hence the maturity of the fetal lungs, can be assessed by observation of stable microbubbles (less than 15 μm diameter). Bubbles are formed by agitation with a Pasteur pipette and examined in hanging drops under the 10 × power of a microscope. Either after a count of bubbles, or after a general survey of hanging drops, the fluid is given a stable microbubble rating. A 'strong' rating indicates that the idiopathic respiratory distress syndrome will not occur after delivery, and that the lecithin/sphingomyelin ratio will indicate maturity. Complete absence of stable microbubbles suggests a high risk of respiratory trouble for the newborn infant, as does a weak or lower rating in the 30 to 37 week gestational age group. The test takes 5 to 10 minutes to perform, is cheap and easy, is not affected by blood, but may be affected by meconium. If a 'strong' rating is found, measurement of the L/S ratio can safely be omitted.

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IF early induction of labour is proposed, it is desirable to assess the risk of idiopathic respiratory distress syndrome (RDS) of the newborn (Avery and Mead, 1959; Pattle *et al*, 1962). When the fetal lungs mature, they discharge surfactant into the amniotic fluid (Fujiwara *et al*, 1964), and this can be estimated in samples obtained at amniocentesis; the lecithin/sphingomyelin (L/S) ratio test (Gluck *et al*, 1974) is the most commonly used. Others are the lecithin assay of Bhagwanani *et al* (1972) and the shake test of Clements *et al* (1972), in which surfactant stabilizes bubbles formed by shaking amniotic fluid with an equal volume of 95 per cent alcohol. The first two take some hours, and all are vitiated if blood or meconium are present. Bubble stability ratio and 'clicking' tests have been investigated by Parkinson *et al* (1974). We describe an alternative test (Pattle *et al*, 1976) which depends on the capacity of the amniotic fluid to form stable bubbles which are 15 μm or less in diameter. The stability of such bubbles depends on the 'surpellic' property of the surfactant, namely its capacity to reduce the net surface tension to a small fraction of its equilibrium value.

DEFINITIONS, MATERIALS AND METHODS

By microbubbles we mean bubbles which are 15 μm or less in diameter. Typically, in a hanging drop, these either disappear in 30 seconds or less, or can remain stable for an hour or more. The latter class we call stable microbubbles.

In this series, idiopathic respiratory distress syndrome (RDS) of the newborn was defined by the presence of two of three signs on the first day after birth, persisting for 24 hours or more. The signs were: a respiration rate of more than 60/minute; expiratory grunting; and costal, intercostal, or sternal retraction. RDS was also confirmed by examination of a chest x-ray for signs of an air bronchogram. Babies fulfilling these criteria usually show hyaline membranes if they die and come to autopsy. Respiratory troubles, not fulfilling the above criteria, are much less related to deficiency of surfactant (see Table I).

A total of 310 specimens of amniotic fluid was examined; 256 samples were obtained by transabdominal amniocentesis for estimation of fetal maturity or investigation of suspected rhesus isoimmunisation, 14 from amniotic fluid draining after rupture of the membranes, 20 at normal delivery, and 20 at Caesarean section. Specimens were collected from three centres. Those with an adverse storage history (more than three months frozen, two weeks liquid at 3°C, or 12 hours at room temperature) were not used.

TABLE I

Relation of stable microbubble rating of amniotic fluid 72 hours or less before delivery to incidence of respiratory distress syndrome (RDS) and other respiratory difficulties in the newborn (214 samples, 37 obtained between 30 to 37 weeks).

	Stable microbubble rating				
	Strong	Medium	Weak	Very weak	Zero
All samples Total (n = 214)	155	23	23	10	3
Incidence of RDS					
No.	1	0	4	4	1
per cent	0·65	0	17·4	40	33
No. with other respiratory difficulties	9	2	2	1	2
30–37 *week group* Total (n = 37)	19	5	6	5	2
Incidence of RDS					
No.	0	0	1	4	1
per cent	0	0	17	80	50
No. with other respiratory difficulties	6	1	0	0	1

Most of the samples were examined after much shorter intervals. The lecithin/sphingomyelin (L/S) ratios were determined by the planimetric method of Gluck *et al* (1974) and classified as: 2 or more (mature), 1·5 to 2 (transitional) and less than 1·5 (immature). In some instances the same experimental method was used but the classification was reported as mature, transitional or immature after comparing the chromatogram with a standard, and without estimation of the L/S ratio. Gestational age was assessed from the last menstrual period or from serial ultrasound measurements, and was confirmed by paediatric assessment.

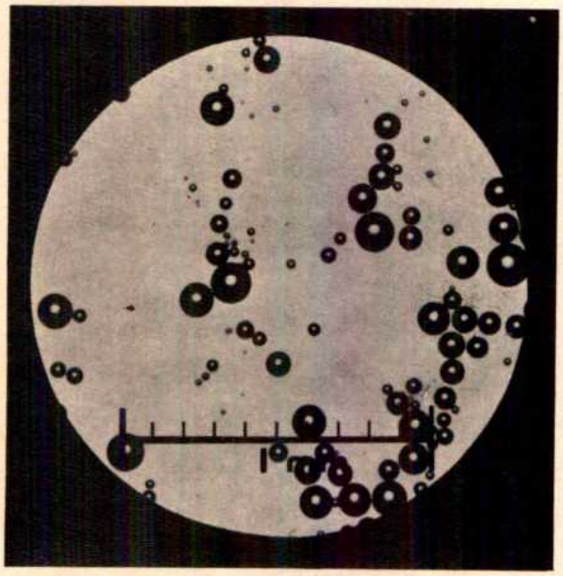

FIG. 1

View of bubble crop in amniotic fluid at lower end of 'strong' stable microbubble rating range (about 20 stable microbubbles/mm^2). Area of field is 2 mm^2.

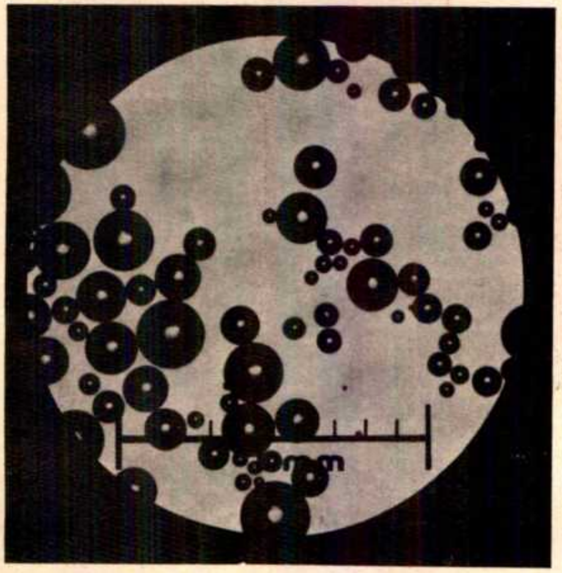

FIG. 2

View of amniotic fluid with no stable microbubbles (zero rated). The few microbubbles present disappeared in a few seconds.

To produce microbubbles the uncentrifuged amniotic fluid was swirled to resuspend sediment. A large drop was placed on a 76 mm x 38 mm microscope slide. A Pasteur pipette, with its tip touching the slide, was held almost vertically in the drop. The drop was sucked into and expelled from the pipette 20 times in quick succession; this process took about 6 seconds, and if correctly done made a characteristic sound; there was a certain knack, easily acquired, in producing a good crop of bubbles such as those seen in Figures 1 and 2. The slide was then immediately inverted over a hollow slide, so that a hanging drop was formed. Two more such slides (or four if the rating appeared weak) were then prepared. The same pipette was used for any one sample, but it was then discarded. The pipettes used (Volac) had a lumen which was 1 mm in diameter, and stems 5 cm long; types with a lumen of 1·5 mm or stem 12 cm long gave poorer bubble crops.

After four minutes, the slides were examined under the 10 × objective of a microscope fitted with an eyepiece graticule. A better view was obtained if the condenser was removed. A fraction of the field of view, containing about 10 to 40 microbubbles, was chosen for counting; at the weaker ratings, the whole field of view (2 mm^2) was used. Counts were made in five such regions in four quadrants of and at the centre of the bubble field; all stable bubbles less than 15 μm in diameter were counted, except those appearing only as black dots and those which were not circular. The bubbles were watched for a few seconds to see if they disappeared (as did the smallest in Fig. 2.) From the figures the mean count of microbubbles/mm^2 on each slide, and a mean for the whole sample, were calculated.

The sample was then given a stable microbubble rating as follows: more than 20 stable microbubbles/mm^2, strong; 10 to 20 stable microbubbles/mm^2, medium; 2 to 10 stable microbubbles/mm^2, weak; less than 2 stable microbubbles/mm^2, very weak; no stable microbubbles, zero.

After some practice, a slide can be given a stable microbubble rating from a general survey, without systematic counting, and this can be recommended for routine use. Figure 1 shows a view of a drop at the lower limit of a 'strong' stable microbubble rating, and Figure 2 a view of a drop of zero-rated amniotic fluid, in which the only microbubbles that can be seen were unstable.

Factors affecting choice of method

The smaller microbubbles travel rather slowly from bottom to top of a hanging drop; delay, after inversion of the slide, allowed for this, and also helped to eliminate unstable bubbles. Except in the strongest samples, bubbles more than 15 μm in diameter tended to be unstable.

Large and small bubbles drifted differently and the distribution of stable microbubbles was very uneven; hence the use of five regions per slide. Slides from the same sample also differed, and so more than one slide was used.

In the physical conditions at the surface of a sessile drop, all microbubbles tend to dissolve; hence the slide had to be inverted immediately. If hollow slides are not available, a 'strong' rating obtained with a naked hanging drop can be trusted.

Chlorhexidine obstetric cream reduced the number of stable microbubbles and slowed the contraction of unstable microbubbles. Slow decay of bubbles was also observed in a mature sample which was cloudy with fat globules; the infant was healthy.

Ten per cent of citrated blood produced no significant reduction in bubble count. With more blood, the fluid itself had also to be citrated to prevent clotting. Fifteen per cent of blood in a mixture halved the bubble count, and 27 per cent reduced it to a quarter. Gluck *et al* (1974) quoted 1·7 per cent of blood as vitiating the L/S ratio test; Clements *et al* (1972) quoted 3 per

TABLE II

Relation of stable microbubble rating to lecithin/sphingomyelin (L/S) ratio, whole series (255 samples).

	Stable microbubble rating				
L/S ratio	Strong	Medium	Weak	Very weak	Zero
Mature	142*	23	25***	8	6
Transitional	5	3	6°	4°	11
Immature	0	2	5*	6*	9

Each asterisk (*) denotes the occurrence of RDS in a baby born within 72 hours of amniotic fluid sampling, while (°) denotes the occurrence of RDS in a baby born more than 72 hours after sampling.

TABLE III

Relation of stable microbubble rating to lecithin/sphingomyelin (L/S) ratio in 129 samples of amniotic fluid obtained by transabdominal amniocentesis at one centre for test of fetal maturity.

	Stable microbubble rating				
L/S ratio	Strong	Medium	Weak	Very weak	Zero
Mature	84	17	14*	2	0
Transitional	0	0	0	1†	0
Immature	0	1	3	6*	1

* One baby born within 72 hours of sampling had RDS

† Baby born more than 72 hours after sampling had RDS.

cent as vitiating the shake test. In our series we included 13 bloodstained samples, out of a total of 310.

Four samples of meconium were examined. One, undiluted, showed a stable microbubble count of 25/mm². Two, after some dilution, showed no stable microbubbles. One, diluted, showed a few stable microbubbles. Samples stained with meconium are therefore suspect. Four out of 310 of our samples (all rated 'strong') were excluded from the analysis on this ground.

Centrifugation reduced the stable microbubble rating of a sample of amniotic fluid. A few specimens in our series had been centrifuged and, using evidence obtained from subsidiary experiments, we multiplied the stable microbubble rating by 3 or 4 to allow for the effect of centrifugation.

A poor bubble crop was often found when the sample contained much debris. Very immature, zero-rated, samples tended to froth excessively, although, when mixed with 95 per cent alcohol in the shake test, they gave a negative result. The stable microbubble rating is quite distinct from the shake test of Clements *et al* (1972) where the observed bubbles were 50 to 500 μm in diameter.

RESULTS

Table I relates the stable microbubble rating of 214 samples of amniotic fluid taken within 72 hours of delivery to the incidence of RDS and other respiratory difficulties. Table II gives the stable microbubble rating of all the samples of amniotic fluid with a known L/S ratio. Table III is similar, but deals only with samples obtained by transabdominal amniocentesis for estimation of fetal maturity at one centre over a period of two years. Table IV shows the relationship between the stable microbubble rating and the shake test in 43 samples so tested. Table V shows the relation of the stable microbubble rating to gestational age; strong ratings were not found before 31 weeks and zero ratings were rare after 37 weeks. Table VI shows the stable microbubble ratings, L/S ratios, and shake test results for the 12 babies with RDS in our series. Four of these showed mature L/S ratios; the

TABLE IV

Relation of stable microbubble rating to results of shake test† in 43 samples.

Shake test	Stable microbubble rating				
	Strong	Medium	Weak	Very weak	Zero
Positive	23	5	3	1	1
Intermediate	4*	0	0	0	0
Negative	0	0	2*	1	3

* One baby born within 92 hours of sampling had RDS.
† Clements *et al* (1972).

TABLE V

Relation of stable microbubble rating to gestational age in 268 samples of amniotic fluid.

Gestational age (weeks)	Stable microbubble rating				
	Strong	Medium	Weak	Very weak	Zero
Less than 26	0	0	0	2	10
26–30	0	0	0	3	10
31–34	7	3	5	8*****°	7*
35–37	17	5	9*	7	2
More than 37	121*	20	24***°	7	1

Each asterisk (*) denotes RDS in a baby born within 72 hours of sampling, while (°) denotes the occurrence of RDS in a baby born more than 72 hours after sampling.

TABLE VI

Stable microbubble rating, lecithin/sphingomyelin ratio, shake test results, and other details relating to babies with RDS

Clinical characteristics	Patient No. 1	2	3	4	5	6	7	8	9	10	11	12
Method of obtaining amniotic fluid (D) at delivery; (A) at amniocentesis	D	D	D	D	A	A	A	A	A	A	A	A
Gestation at sampling (weeks)	33	34	31	32	34	39	36	38	38	39	38	32
Stable microbubbles/mm^2	0	x	0·1	0·3	0·4	2·2	3·2	4·9	6	182	4·2	0·4
Stable microbubble rating	Zero	very weak	very weak	very weak	very weak	weak	weak	weak	weak	strong	weak	very weak
L/S ratio	x	x	x	x	immature	immature	mature	mature	mature	mature	trans.	trans.
Shake test	x	x	x	x	x	negative	x	x	x	intermediate	x	x
Sampling to delivery interval if more than 72 hours (days)	—	—	—	—	—	—	—	—	—	—	10	16
Severity of RDS (mild +, moderate ++, severe +++).	+++[a]	+	++	+	+	+	++	+	+	+[b]	died[c]	+

[a] Diabetic mother [b] Rhesus incompatibility [c] Hyaline membranes present x Unknown or uncertain

total number of samples with a mature L/S ratio within 72 hours of the birth of the infant was 164. Thus the incidence of RDS with a mature L/S ratio was 2·4 per cent.

One baby with RDS (No. 10) had had a 'strong' amniotic fluid stable microbubble rating. This baby had mild RDS of 24 hours duration and an L/S ratio of 2·4; a chest x-ray showed that atelectasis was confined to the upper lobe of the left lung. It is unlikely that examination of amniotic fluid would detect a deficiency of surfactant in one lobe only. It may well be that such cases are much rarer than the 1 in 12 found here, but Howatt *et al* (1965) found that surface properties developed earlier in the upper than in the lower parts of fetal sheep lungs, and Bozic (1963) described a case of hyaline membrane disease in which a part of one lobe, abnormally vascularised from the aorta, was fully aerated.

DISCUSSION

Except in patient No. 10, RDS did not occur in conjunction with a 'strong' stable microbubble rating (Table I). Table I also shows that a zero stable microbubble rating was predictive of respiratory difficulty. At 30 to 37 weeks gestational age, we found a high (46 per cent) incidence of RDS associated with weak or lower stable microbubble ratings. Clements *et al* (1972) found 53 per cent of cases in this gestational age-group when the shake test on amniotic fluid gave an intermediate or negative result. Other respiratory difficulties appeared to show no relation to stable microbubble rating unless the rating was zero.

Tables II and III show that only a small minority (3·6 per cent) of amniotic fluid samples with a 'strong' stable microbubble rating had an L/S ratio which was not mature, and none of these was in our group of samples taken by transabdominal amniocentesis to assess fetal maturity (Table III). However, of the samples obtained by amniocentesis and with mature L/S ratios, 28 per cent showed a stable microbubble rating which was less than 'strong'. As 65 per cent of this group showed a 'strong' rating, this suggests that assessment of the stable microbubble ratings could eliminate the need for determination of many L/S ratios.

It is harder to compare the stable microbubble rating test with the shake test, as we only did 43 of the latter in our series. Those patients with a positive shake test included 30 per cent with less than 'strong' microbubble rating (Table IV) and, in a completely separate series (Parkinson, 1977), 17 per cent with a positive shake test were found to have a less than mature L/S ratio. The categories 'mature L/S ratio' and 'positive shake test' thus include patients who do not have a 'strong' stable microbubble rating, and so 'strong' stable microbubble rating is a surer index of lung maturity than are the other two tests.

The one baby with RDS (No. 10) who had a 'strong' amniotic fluid stable microbubble rating also showed a mature L/S ratio. In a survey of the world-wide results of the L/S ratio and shake tests (Parkinson and Harvey, 1978), incidences of 1·5 per cent RDS among cases with mature L/S ratio (in our series, 2·4 per cent), and 1 per cent among those with positive shake test were found. The value of 0·6 per cent RDS among those with 'strong' stable microbubble ratings (Table I) compares well with these figures. For closer comparison of the stable microbubble ratings with the other tests, data about more pregnancies ending in the birth of an infant which develops RDS are needed. Stable microbubble rating of amniotic fluid would seem to be a useful and rapid test for fetal lung maturity.

To grade the microbubble rating as 'strong', 'less than strong', or 'zero' is all that is necessary, and this can be done by a general survey of the slides without resort to systematic counting. The 'strong' rating takes five minutes to recognize, while a zero rating takes ten minutes, which is still much less time than that required to measure the L/S ratio, or do a shake test. The stable microbubble rating is unaffected by amounts of blood which vitiate the other two tests. We propose its evaluation on pharyngeal (Weller *et al*, 1976) and gastric (McClure *et al*, 1975) aspirates from the newborn as a means of predicting the occurrence of RDS.

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ULTRASOUND ASSESSMENT OF FETAL GROWTH

BY

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Summary

Consecutive ultrasonic measurements of the fetal head area, thorax area, abdomen area, head/thorax (H/T) area ratio and head/abdomen (H/A) area ratio were obtained from 100 patients with a normal pregnancy and from 186 patients with suspected intrauterine fetal growth retardation. Of all the measurements used, H/A area ratio was found to be most accurate in identifying intrauterine fetal growth retardation predicting 82·9 per cent at 33 weeks and 85·7 per cent at 36 to 38 weeks of gestation. This technique was also found to be useful in distinguishing between the two types of growth retardation. The H/A area ratio was helpful in identifying the growth acceleration pattern of a large baby.

GOLDSTEIN AND PECKHAM (1975) have shown that birth weight is the principal variable affecting late fetal and neonatal mortality and that low birth weight babies, both pre-term and light-for-dates, are at greatest risk of anoxic stillbirth and neonatal death. In a series of 44 256 consecutive births from 1958 to 1971, Usher and McLean (1974) found a two-fold increase in the perinatal mortality for babies born more than 2 SDs below mean weight over those whose birth weight was within 2SD of the mean. To improve the existing mortality and morbidity associated with a growth retarded fetus, appropriately timed delivery with intensive intrapartum and neonatal care is necessary. From ultrasound cephalometry it would appear that attempts to predict birth weight from a single measurement of the biparietal diameter are of little value (Varma, 1974). It has been shown that a growth retarded baby has a compensatory ability to continue with normal brain growth, at the expense of body growth. Attention has therefore been directed recently to ultrasound measurements of circumference or area of fetal head, thorax and abdomen, and total uterine volume in relation to fetal growth retardation (Levi, 1972; Hansmann *et al*, 1973; Campbell and Wilkin, 1975; Higginbottom *et al*, 1975; Kurjak and Breyer, 1976; Lunt and Chard, 1976; Wladimiroff *et al*, 1977).

The object of this study was to compare the value of antenatal measurements of the fetal head area, the thorax area, the abdomen area, and the head to thorax and head to abdomen area ratios as indices of fetal growth *in utero*.

METHODS

All ultrasound measurements were made from B-scan echograms obtained with the diasonograph 4102 (Nuclear Enterprises Limited, Edinburgh) using a frequency of 2·5 MHz and a velocity setting of 1540 m/s. Measurements of the biparietal diameter (BPD) were made by the combined A and B scan method described by Campbell (1968).

The head area was measured from the plane of the measured BPD. The thoracic area was measured from the plane at right angles to the fetal spine at the level of the heart when the maximum movement of one of the valves, either mitral or tricuspid, was identified (Schlensker and Bolte, 1973). Longitudinal scans were made to identify the fetal abdominal aorta or the fetal spine and scans were then made orthogonal to the long axis of the fetal body until the appearance of the umbilical vein as it passed under the fetal liver to measure the abdominal area. When the fetal spine was anterior, the fetal stomach was identified to take the cross section of the fetal upper abdominal area. All areas were measured using a planimeter from polaroid photographs after making the appropriate corrections.

Patients

The study was arranged in two parts. In the first part (normal series), serial measurements of the fetal head area, the thorax area, the abdomen area, the head to thorax and the head to abdomen area ratios were obtained from 100 normal patients of known maturity with an uncomplicated pregnancy who were delivered of an infant whose weight was on the tenth centile or above, standardised for maternal parity, sex of the infant and the duration of gestation (Thomson *et al*, 1968). Maturity of the fetus was confirmed in all patients using cephalometry in the early second trimester.

Similar measurements were made in pregnancies with suspected fetal growth retardation ('at risk' series). This group consisted of 186 patients, of whom 35 were delivered of a light-for-dates infant. An infant was considered light-for-dates if its birth weight was below the tenth centile standardised for its maturity, maternal parity and sex of the infant (Thomson *et al*, 1968). Statistical differences between the two groups were termed by Student's 't' test.

RESULTS

Table I shows the pregnancy complications and the number of normal weight and light-for-dates infants in the 'at risk' series.

Of the 35 infants, 26 (74·3 per cent) had a birth weight at or below the fifth centile, and 9 (25·7 per cent) had a birth weight above the fifth centile, but below the tenth centile.

TABLE I

Complications of pregnancy in the 'at risk' series

	Normal infant weight group	Light-for-dates group
Pre-eclampsia	30	5
Hypertension	25	4
Static weight	30	3
Subfertility	18	0
Clinical growth retardation	15	16
Antepartum haemorrhage	6	1
Elderly multigravidae	6	1
Elderly primigravidae	6	0
Bad obstetric history	3	2
Previous neonatal death	2	1
Previous stillbirth	5	1
Diabetes	1	0
Premature labour	2	0
Urinary tract infection	2	0
Alcoholic	0	1
Total	151	35

Head area

Normal data. Figure 1 shows the mean, 5th and 95th per cent confidence limits for the fetal head area for each week of gestation from 26 to 40 weeks. The growth of the head area was fairly rapid up to 35 weeks after which there was a gradual reduction in rate up to 40 weeks of gestation.

Fetal growth retardation. Figure 1 shows a significant difference between the mean head areas for the normal series and light-for-dates group in the 'at risk' series from 35 weeks onwards ($p < 0.01$). When one measurement of the head area was taken 10 days before delivery, 74·3 per cent of the light-for-dates infants were identified, whereas if the head area measure-

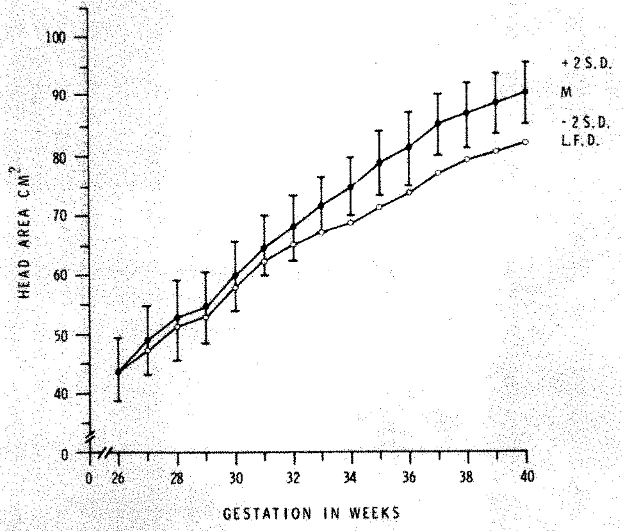

FIG. 1

Mean head area (± 2SD) for the normal series (●——●) and mean head area for the light-for-dates infants (○——○) in the 'at risk' group between 26 and 40 weeks gestation

TABLE II

Comparison of various measurements in the detection of fetal intrauterine growth retardation (IUGR)

		IUGR Detection		False negative result		False positive result	
		No.	Per cent	No.	Per cent	No.	Per cent
Head area	within 10 days of delivery	26	74·3	9	25·7	16	10·6
	at 33 weeks	20	57·0	15	43·0	16	10·6
Thoracic area	within 10 days of delivery	29	82·9	6	17·1	13	8·6
	at 33 weeks	25	71·4	10	28·6	16	10·6
Abdomen area	within 10 days of delivery	29	82·9	6	17·1	12	7·9
	at 33 weeks	28	80·0	7	20·0	15	9·9
H/T area ratio	within 10 days of delivery	29	82·9	6	17·1	12	7·9
	at 33 weeks	27	77·1	8	22·9	13	8·6
H/A area ratio	within 10 days of delivery	30	85·7	5	14·3	13	8·6
	at 33 weeks	29	82·9	6	17·1	12	7·9

ment was taken at 33 weeks gestation, only 57 per cent of the light-for-dates infants were identified. The incidences of false negative results at 33 weeks and at 10 days before delivery were 43 per cent and 25·7 per cent respectively. The incidence of false positive results remained the same (Table II). In the light-for-dates group when the head area was plotted against the birth weight of the infant born within 10 days of the measurement, the correlation was not significant (Fig. 2).

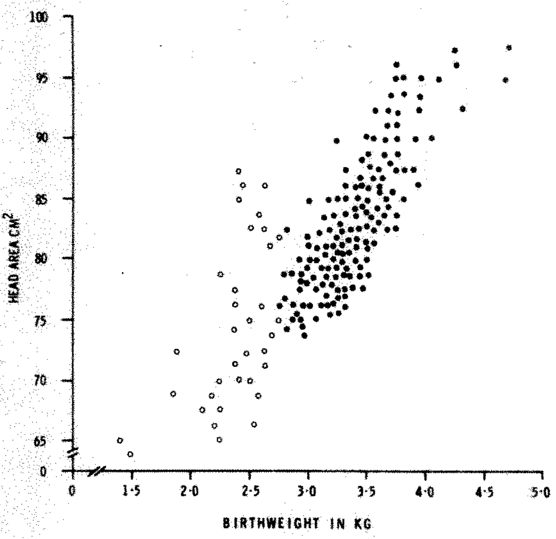

FIG. 2

Relation between the fetal head areas measured within 10 days of delivery and the birth weight of infants in the 'at risk' group.

○ Light-for-dates.
● Others

Thorax area

Normal data. Figure 3 shows the mean, 5th and 95th per cent confidence limits for the fetal thorax area for each week of gestation from 26 to 40 weeks. The thorax area increased steadily up to 37 weeks gestation after which there was a gradual reduction in the growth rate.

Fetal growth retardation. The difference between the mean thorax areas for the normal series and the light-for-dates group in the 'at risk' series (Fig. 3) was statistically significant from 34 weeks onwards ($p < 0 \cdot 01$). In the light-for-dates group, thorax area measurements plotted against the birth weight of the infants born within ten days of measurements showed good correlation (Fig. 4). Table II shows that a single thoracic area measurement at 33 weeks and at ten days before delivery enabled identification of 71·4 per cent and 82·9 per cent respectively of light-for-dates babies. The incidence of false

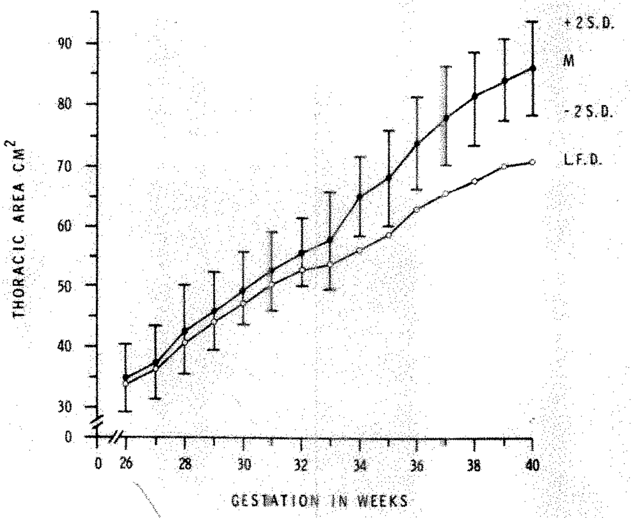

FIG. 3

Mean thorax area (± 2SD) for the normal series (●——●) and mean thorax area for light-for-dates infants (○——○) in the 'at risk' group between 26 and 40 weeks gestation.

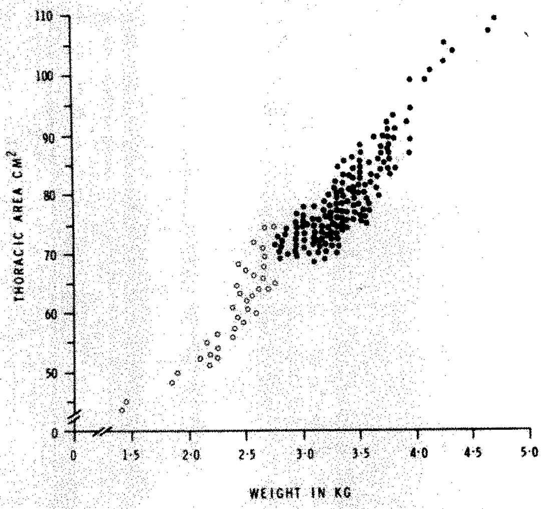

FIG. 4

Relation between the fetal thorax areas measured within 10 days of delivery and the birth weight of infants in the 'at risk' group.

○ Light-for-dates
● Others

negative results was 28·6 per cent at 33 weeks compared with 17 per cent at 10 days before delivery. The incidence of false positive results was low.

Abdomen area

Normal data. The mean, 5th and 95th per cent confidence limits for the fetal abdomen area in relation to gestational age are shown in Figure 5. The growth of the abdomen area was steady up to 40 weeks gestation.

Fetal growth retardation. Figure 5 shows the difference in the means for the normal series and the light-for-dates group in the 'at risk' series from 33 weeks onwards. This was statistically significant from 32 weeks onwards ($p < 0{\cdot}01$). In the light-for-dates group, the abdomen areas plotted against the birth weight of infants born within ten days of measurement showed good correlation (Fig. 6). Table II shows that the accuracy of identifying light-for-dates infants using the abdomen area was 80 per cent at 33 weeks and 83 per cent at 10 days before

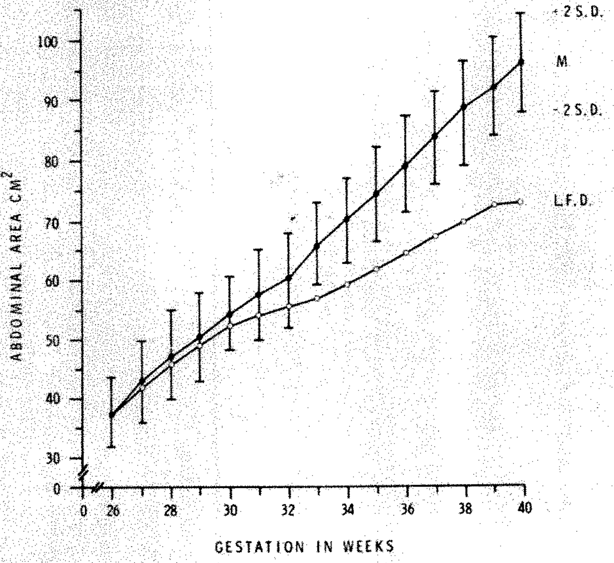

FIG. 5

Mean fetal abdomen area (± 2SD) for the normal series (●——●) and mean abdomen area for the light-for-dates infants (○——○) in the 'at risk' group between 26 and 40 weeks gestation.

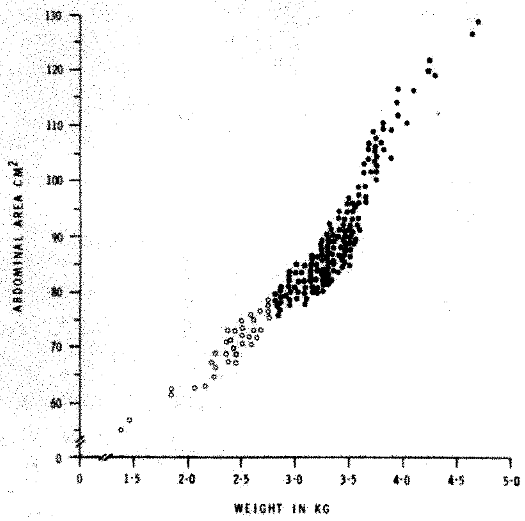

FIG. 6

Relation between the fetal abdomen areas measured within 10 days of delivery and the birth weight of infants in the 'at risk' group.

○ Light-for-dates
● Others

delivery. The incidences of false negative results were 20 per cent and 17 per cent respectively. The incidence of false positive results was low.

Head to thorax (H/T) area ratio

Normal data. Figure 7 shows the mean, 5th and 95th per cent confidence limits for the H/T area ratio in relation to gestational age. The fetal H/T area ratio in normal pregnancy shows a reduction from 1·25 at 26 weeks to 1·05 at 40 weeks gestation.

Fetal growth retardation. The difference between the mean H/T area ratio for the normal series and light-for-dates group in the 'at risk' series was found to be statistically significant from 33 weeks onwards ($p < 0{\cdot}01$; (Fig. 7). In the light-for-dates group, H/T area ratio plotted against the birth weight of the infants born within ten days of the measurement showed good correlation (Fig. 8). A single measurement of H/T area ratio identified 77 per cent of light-for-dates infants at 33 weeks and 83 per cent within 10 days before delivery. The incidences of false negative results were 23 per cent and 17 per cent respectively. The incidence

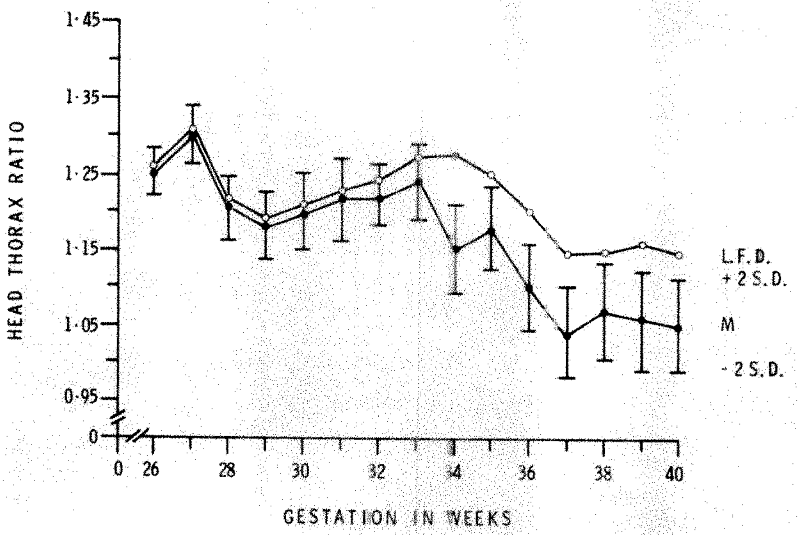

FIG. 7

Mean head to thorax area ratio (± 2SD) for the normal series (●———●) and mean head to thorax area ratio for the light-for-dates infants (○———○) in the 'at risk' group between 26 and 40 weeks gestation.

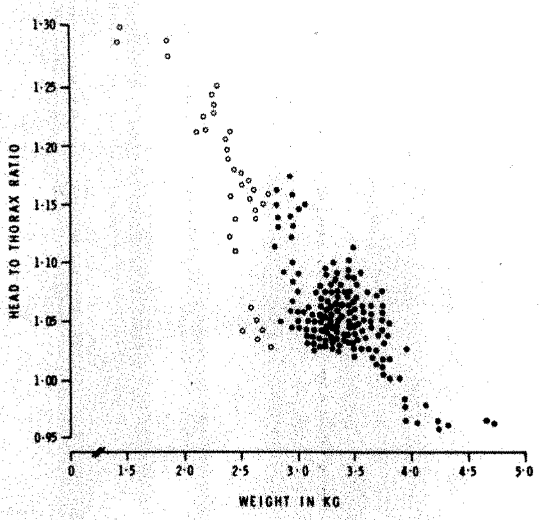

FIG. 8

Relation between the head to thorax area ratios measured within 10 days of delivery and the birth weight of infants in the 'at risk' group.

○ Light-for-dates
● Others

of false positive results remained low (Table II).

Head to abdomen (H/A) area ratio

Normal data. The mean, 5th and 95th per cent confidence limits for the fetal H/A area ratio in relation to gestational age are shown in Figure 9. In normal pregnancy the H/A area ratio decreased from 1·20 at 26 weeks to 0·92 at 40 weeks of gestation.

Fetal growth retardation. The difference in the mean H/A area ratio for the normal series and the light-for-dates group in the 'at risk' series was significant from 32 weeks onwards ($p < 0 \cdot 01$). In the light-for-dates group, the H/A area ratio plotted against the birth weight of the infants born within 10 days of the measurement showed good correlation (Fig. 10). Table II shows that the H/A area ratio was the best measurement for identifying intrauterine fetal growth retardation. One measurement of H/A area ratio identified 82·9 per cent of light-for-dates infants at 33 weeks and 85·7 per cent within 10 days of delivery. The incidences of false negative results were 17·1 per cent and

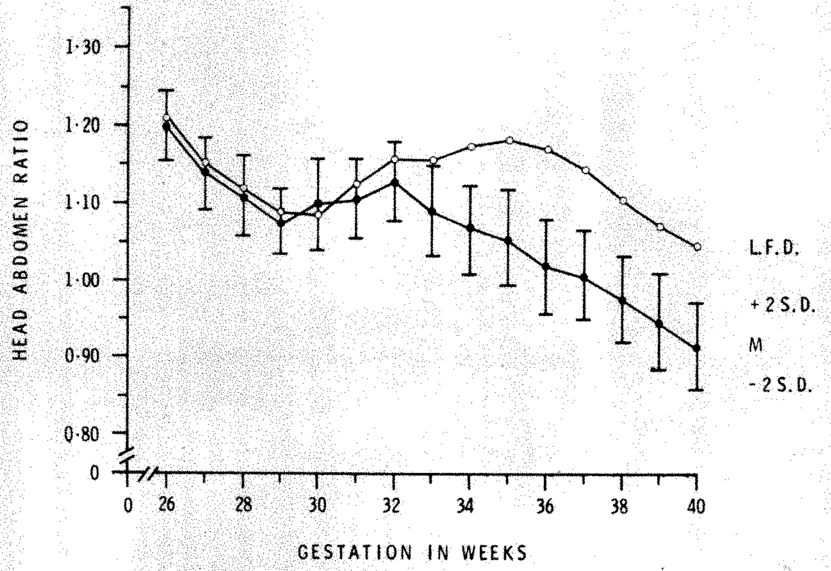

FIG. 9

Mean head to abdomen area ratio (± 2SD) for the normal series (●———●) and mean head to abdomen ratio for the light-for-dates infants (○———○) in the 'at risk' group between 26 and 40 weeks gestation.

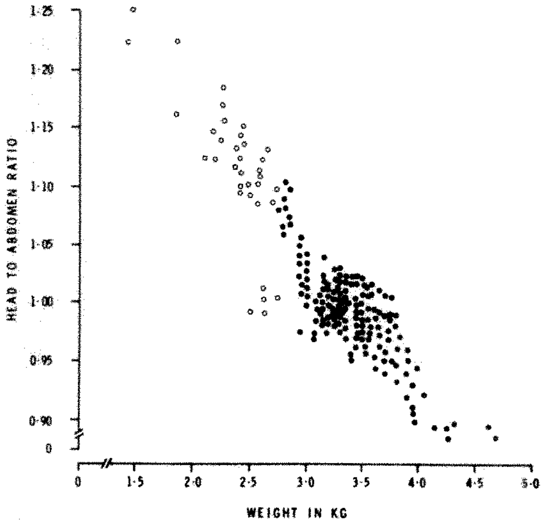

FIG. 10

Relation between head to abdomen area ratio measured within 10 days of delivery and the birth weight of infants in the 'at risk' group.

○ Light-for-dates
● Others

14·3 per cent respectively. The false positive results were low.

DISCUSSION

Prediction of birth weight by ultrasound measurements of fetal body sections was recommended by Thompson *et al* (1965), Garrett and Robinson (1971), Hansmann *et al* (1973), Campbell (1974), Campbell and Wilkin (1975), Kurjak and Breyer (1976) and Campogrande *et al* (1977). Thompson *et al* (1965) and Hansmann *et al* (1973) found that thoracic measurements predicted fetal weight within ± 500 g of the actual weight in 80 per cent of babies. Campbell and Wilkin (1975) and Kurjak and Breyer (1976) found that fetal abdominal circumference at the level of umbilical vein had a good correlation with birth weight.

Our study showed that a single measurement of the head area at 33 weeks identified only 57 per cent of the light-for-dates infants, compared with 74·3 per cent when the measurement was taken within 10 days before delivery at 36 to 38 weeks of gestation. Using thoracic area measurements improved reliability and it was then possible to identify 71·4 per cent of the light-for-dates infants at 33 weeks and 82·9 per cent at 10 days before delivery. The abdomen area measurements identified 80 per cent of the light-for-dates fetuses at 33 weeks and 82·9 per cent at 10 days before delivery. Campbell and Wilkin (1975) showed that measurements of the circumference of the fetal abdomen at 32 weeks and at 36 weeks, identified 87 per cent and 75 per cent of light-for-dates infants respectively. As the fetal liver is the most severely affected organ in fetal growth retardation associated with utero-placental insufficiency, the circumference or area of the fetal abdomen is of great importance in the assessment of fetal nutrition.

Campbell and Thoms (1977) and Wladimiroff *et al* (1977) suggested that not all the light-for-dates infants were the result of utero-placental insufficiency, and that a small group of infants remain small with low growth potential from the beginning of the pregnancy. It is not possible to identify these two groups of growth retarded infants using only area or circumference of the cross-sections of the fetal body. Campbell and Thoms (1977) reported that H/A circumference ratio was useful in identifying the two groups of intrauterine fetal growth retardation, whereas Wladimiroff *et al* (1977) used H/T area ratio to differentiate the two groups of intrauterine growth retardation.

Using the H/T area ratio, we could identify 77 per cent of the light-for-dates infants at 33 weeks and 83 per cent at 10 days before delivery. Of the 35 light-for-dates infants, 29 had a H/T area ratio above the 95th per cent confidence limits. These babies had small head and small thoracic areas, but the head area was relatively larger than the thoracic area, possibly due to the brain-sparing effect. Four of the 35 light-for-dates infants, with a H/T area ratio around the mean, had small head and small thoracic areas in proportion; two of these four babies had multiple congenital abnormalities not identifiable on ultrasound examinations. The remaining 2 infants had a H/T area ratio just below the 95th per cent confidence limits and also had a small head and thoracic area, but the head area was relatively larger than the thoracic area, suggesting a brain-sparing effect. The H/T area ratio was found to be low in 10 of 151 infants with normal weight in the 'at risk' series. These 10 babies whose birth weight was above the 90th centile had larger head and thoracic areas with the thoracic area relatively larger than the head area, suggesting a pattern of growth acceleration. Our results confirmed those of Wladimiroff *et al* (1977) that the H/T area ratio was useful not only in identifying fetal growth retardation as early as 33 weeks, but also in identifying the two types of intrauterine growth retardation.

The H/A area ratio identified 83 per cent of the light-for-dates infants at 33 weeks and 85·7 per cent at 10 days before delivery. Of the 35 infants, 30 had a H/A area ratio above the 95th per cent confidence limits, one had a H/A area ratio below the 95th per cent confidence limits. These 31 infants had asymmetrical growth retardation. Four of 35 (11·4 per cent) infants who had a H/A area ratio around the mean had symmetrical growth retardation from causes other than utero-placental insufficiency. Ten of 151 infants (6·6 per cent) had a low H/A area ratio suggesting the growth acceleration pattern of large babies with birth weight above the 90 per cent confidence limits. Our results confirmed those of Campbell and Thoms (1977) that H/A area ratio is one of the most reliable methods of identifying the two groups of intrauterine growth retardation during the early third trimester.

Asymmetrical growth retardation had been observed in experimental studies on impairment of vascular blood supply to the fetus in rats (Wigglesworth, 1964), sheep (Creasy *et al*, 1972) and in monkeys (Hill, 1974). In these studies brain to body ratio was elevated suggesting a brain-sparing effect. This may be due to the preferential redistribution of well-oxygenated blood to the fetal brain. Symmetrical growth retardation is considered the outcome of a reduced growth potential as observed in malnourished rats (Winick, 1971) and guinea pigs. In the human fetus, this type of growth retardation is seen after viral infection in early pregnancy and in the presence of chromosomal aberrations. There is a permanent loss of cells and the fetal brain is not spared. The prognosis and outcome for these two types of infants are different.

Finally, we conclude that a single measurement of fetal abdomen area and the H/A area ratio appears to be the most reliable and efficient method of identifying intrauterine fetal growth retardation. The optimal method of screening all the 'at risk' pregnancies would be the combination of an early determination of fetal maturity combined with a late measurement of the fetal abdomen at 32 to 33 weeks of gestation, and a repeat measurement between 36 and 38 weeks of gestation to identify intrauterine fetal growth retardation. At the same time, H/A area ratio would provide a method to identify the type of growth retardation which is important in the further management of the pregnancy.

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BLOOD PRESSURE CHANGES WHEN UTERINE STIMULANTS ARE USED AFTER NORMAL DELIVERY

BY

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AND

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Summary

Use of an automatic sphygmomanometer showed that intravenous ergometrine given immediately after delivery caused significant elevation of diastolic blood pressure in all 10 normotensive women studied. Blood pressure was also raised in some patients following the use of intramuscular oxytocin and ergometrine (Syntometrine). Uterine stimulants for use after delivery must be chosen with care.

THE effects of ergot on the pregnant uterus have been known, if not understood, for hundreds of years (Moir, 1964). Ergot also has a constrictor effect on arterial blood vessels as first described by Dale (1906). Occasional reports of severe rises in blood pressure following clinical use of ergot preparations has led to a general awareness of the hazards of these drugs in patients with hypertension (Baillie, 1963).

Ergometrine, alone or with synthetic oxytocin, has been widely used in management of the third stage of labour. The dangers associated with these drugs have received some attention (Friedman, 1957; Ringrose, 1962; Browning, 1974); but there is little information on changes of blood pressure following their use, mainly because of the difficulty of obtaining frequent blood pressure recordings by a reliable, non-invasive method.

This paper describes an investigation of the effects of parenteral uterine stimulants on the blood pressure of normotensive women in the immediate postpartum period, using an automatic sphygmomanometer as previously described (Biggs, 1975).

MATERIALS AND METHODS

Twenty-six women who were delivered at the Royal Women's Hospital, Brisbane were studied. All were normotensive, with no blood pressure recordings greater than 130/80 mm Hg during pregnancy or labour. Spontaneous vaginal delivery took place and postpartum blood loss was less than 200 ml in each patient. Details of prior drug therapy and duration of labour were recorded for each patient.

Peripheral blood pressure was measured with the Arteriosonde 1217 (Roche, Medical Electronics Division). The instrument provides automatic inflation of a standard sphygmomanometer cuff at predetermined time intervals. During deflation of the cuff the pulse wave in the underlying brachial artery is detected by ultrasonic sensors. Electronic filters cause rejection of signals resulting from arm movements or other extraneous influences. Mercury manometers on the machine show systolic and diastolic pressures, the latter corresponding to the point of muffling—the so-called Korotkoff phase IV (Pickering, 1968). Valid measurements of systolic and diastolic pressures are marked on a direct reading, variable-speed recorder.

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The equipment was explained to each patient and informed consent for the procedure obtained. The need for her to maintain the same position during recordings was stressed. Following delivery and birth of the placenta, the patients were swabbed down and the bed linen changed. In one patient an episiotomy was repaired because of bleeding; in all other patients recording of blood pressure was commenced within 10 minutes of delivery.

A baseline of systolic and diastolic blood pressures was obtained by calculating the mean and standard deviation (SD) of 6 to 10 readings. At approximately 20 minutes after delivery, treatment was given as follows. A control group was given no uterine stimulants; patients in a second group were given an intramuscular injection of synthetic oxytocin, 5 iu, and ergometrine maleate, 0·5 mg (syntometrine: Sandoz); and patients in a third group were given an intravenous injection of ergometrine maleate, 0·5 mg. No other drugs were given during the recording period, which lasted for at least 30 minutes. Postpartum blood loss was invariably less than 200 ml.

Successive blood pressure measurements were grouped into 5 to 6 minute periods for the purpose of calculating mean levels and SD. The statistical significance of any changes of mean systolic and diastolic pressures from baseline levels was determined by application of Students 't' test. The direction and extent of changes of blood pressures were noted, together with their duration.

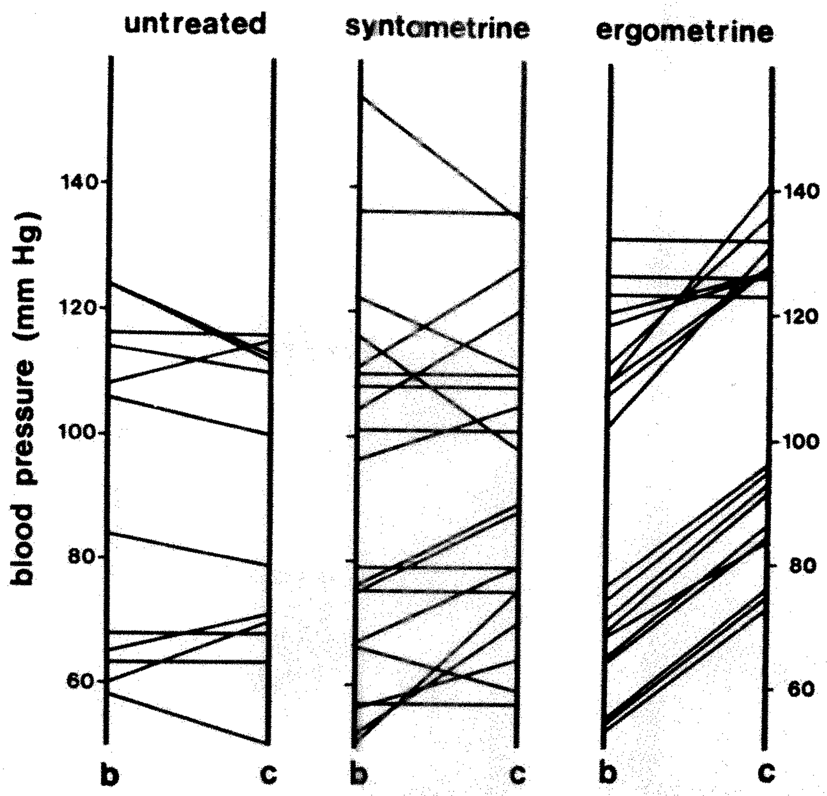

FIG. 1

Blood pressure changes after uterine stimulants in parturient women. Baseline levels (b) are the means of 6 to 10 recordings at one-minute intervals; (c) shows the maximum deviation from baseline of means of groups of 5 to 6 successive recordings in the 30 minutes after baseline.

RESULTS

The mean baseline pressures in the untreated, syntometrine-treated and ergometrine-treated groups were almost identical. Systolic pressures were 115 ± 8 (SD), mm Hg, 115 ± 15 mm Hg and 116 ± 9 mm Hg respectively. The mean baseline diastolic pressures in the groups were 66 ± 9 mm Hg, 65 ± 11 mm Hg and 65 ± 8 mm Hg respectively. Women who smoked more than 10 cigarettes per day numbered 1 of 6 in the untreated group, 3 of 10 in the syntometrine-treated group and 2 of 10 in the ergometrine-treated group. Analgesia, consisting of an intramuscular injection of pethidine, 100 mg, and droperidol, 5 mg, was given within the four hours prior to pressure recording in 2 of the 6 untreated women and 6 of the 10 women in each of the two treatment groups.

The blood pressure changes are shown in Table I and Figure 1.

In the untreated group, mean systolic pressure rose in one patient and fell in four; mean diastolic pressure rose in two patients and fell in two; there was no significant change in the remaining patients. In the syntometrine-treated group, mean systolic pressure rose in three patients and fell in three; mean diastolic pressure rose in six patients and fell in one; other

TABLE I

Details of blood pressure changes after delivery in normotensive women.

Patient No. and Treatment	Baseline pressures (mm Hg) Systolic Mean ± SD	Baseline pressures (mm Hg) Diastolic Mean ± SD	Maximum change in pressure (mm Hg) Systolic	Maximum change in pressure (mm Hg) Diastolic	Onset of change (minutes) Systolic	Onset of change (minutes) Diastolic	Duration of change (minutes) Systolic	Duration of change (minutes) Diastolic
Untreated								
1	124 ± 3	65 ± 5	−11	+ 6	5	15	> 50	> 30
2	124 ± 4	84 ± 4	−12	− 5	10	10	20	10
3	106 ± 5	58 ± 6	− 6	− 8	20	20	> 20	10
4	114 ± 3	63 ± 3	− 4	N.S.	15	—	10	—
5	116 ± 7	68 ± 4	N.S.	N.S.	—	—	—	—
6	108 ± 7	60 ± 4	+ 7	+10	40	20	> 20	> 40
*Syntometrine**								
7	108 ± 7	57 ± 6	N.S.	N.S.	—	—	—	—
8	116 ± 6	66 ± 7	−18	− 7	5	10	5	5
9	111 ± 5	76 ± 3	+16	+13	10	10	> 25	> 25
10	101 ± 4	52 ± 4	N.S.	+18	—	5	—	> 30
11	122 ± 2	75 ± 5	−11	N.S.	5	—	25	—
12	136 ± 5	67 ± 5	N.S.	+12	—	20	—	> 15
13	110 ± 7	50 ± 3	N.S.	+25	—	10	—	> 35
14	96 ± 6	56 ± 4	+ 9	+ 8	10	30	10	> 5
15	104 ± 3	79 ± 4	+16	N.S.	5	—	> 30	—
16	154 ± 5	75 ± 7	−19	+13	5	25	> 35	10
Ergometrine†								
17	112 ± 5	76 ± 11	+24	+20	5	5	10	30
18	107 ± 4	74 ± 4	+21	+21	5	5	> 30	> 30
19	120 ± 4	53 ± 8	+ 7	+20	10	15	15	20
20	123 ± 11	69 ± 5	N.S.	+23	—	5	—	> 55
21	109 ± 9	65 ± 5	+19	+22	5	5	25	> 30
22	126 ± 5	54 ± 3	N.S.	+21	—	5	—	100
23	132 ± 13	54 ± 5	N.S.	+22	—	10	—	> 35
24	102 ± 5	64 ± 4	+30	+21	5	5	> 35	> 35
25	109 ± 8	71 ± 5	+32	+22	5	10	> 65	60
26	118 ± 4	69 ± 1	+10	+15	5	5	> 30	20

*Synthetic oxytocin, 5 iu, and ergometrine maleate, 0·5 mg, by intramuscular injection.

† Ergometrine maleate, 0·5 mg, intravenously.

N.S. = Not significant.

blood pressure recordings showed no significant change. In the ergometrine-treated group mean systolic pressure rose in seven patients and showed no change in three patients; mean diastolic pressure rose in all ten patients.

In the untreated group, two patients showed elevation of diastolic pressure for more than 30 minutes. In the syntometrine-treated group, 4 of the 6 women with raised diastolic pressure showed this change for more than 15 minutes. In the ergometrine-treated group diastolic elevation continued for at least 20 minutes in all ten patients. Elevated diastolic pressure was observed for 100 minutes in one patient.

DISCUSSION

The routine use of oxytocic drugs in the management of the third stage of labour has won wide acceptance. One of the most commonly used preparations is synthetic oxytocin, 5 iu with ergometrine maleate, 0.5 mg, (Syntometrine) given by intramuscular injection. Ergometrine, 0·5 mg, by intravenous injection has also been used, especially when a more rapid effect has been sought.

The principal complication of ergot preparations in the immediate postpartum period is hypertension (Hendricks and Brenner, 1970). The present study shows that blood pressure rises are common after intravenous ergometrine, all of the patients tested having significant diastolic elevations. The changes occur rapidly, usually within one minute, and may last for longer than an hour. Intramuscular syntometrine has less effect on blood pressure. Elevations of either systolic or diastolic pressure occurred in 6 of 10 patients, but the onset of change was slower, and the magnitude of change was generally less.

Blood pressure changes in normotensive patients given neither oxytocic nor ergot alkaloid in the immediate postpartum period were variable. Only 2 of the 6 patients in the control group showed a rise in systolic or diastolic pressure, and the maximum rise was only 10 mm Hg.

None of the women smoked during labour or during the present studies. However, smokers (defined as women who smoked more than ten cigarettes/day during pregnancy) were distributed in all groups and smoking habits did not appear to influence the results. Neither duration of labour nor analgesic and sedative drugs given within four hours of delivery appeared to affect postpartum blood pressure changes.

This study confirms the generally held impression that intravenous ergometrine causes significant blood pressure elevation in normal parturient women. An intramuscular injection of oxytocin and ergometrine is a safer alternative for routine use.

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THE COMPOSITION OF AMNIOTIC FLUID IN PREGNANCIES COMPLICATED BY FETAL ANENCEPHALY OR SPINA BIFIDA

BY

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Summary

The concentration of amniotic fluid glucose, total protein, sodium, potassium, calcium, magnesium and phosphate as well as amniotic fluid osmolality were measured in normal second trimester pregnancies and in second trimester pregnancies complicated by fetal anencephaly or spina bifida. Amniotic fluid glucose concentration was low in anencephaly, while phosphate and total protein were high; calcium concentration and osmolality were slightly elevated with spina bifida. The application of these findings to antenatal diagnosis are discussed.

THERE has been much emphasis recently on the development of methods for the antenatal detection of neural tube defects, mainly by the measurement of alpha-fetoprotein concentration in maternal plasma and amniotic fluid. It would be most desirable if the measurement of other constituents of amniotic fluid were to produce a lower incidence of misleading results and useful if it were possible to distinguish between anencephaly and spina bifida.

The composition of amniotic fluid is determined in part by the fetus it surrounds (Seeds, 1974) and so in anencephaly, where there is gross dysfunction of the hypothalamic-pituitary axis, the amniotic fluid could have a characteristic chemical profile. With this possibility in mind and as part of a wider antenatal diagnosis programme of research, we decided to investigate in detail the composition of amniotic fluid in pregnancies complicated by neural tube defects.

Our finding of low amniotic fluid glucose concentration with fetal anencephaly has already been reported (Pettit *et al*, 1977), and the concentrations of a number of constituents of normal amniotic fluid have been documented (Benzie *et al*, 1974; Gillibrand, 1969; Sinha and Carlton, 1970). In this study, we measured glucose, total protein, sodium, potassium, magnesium, calcium, phosphate and osmolality in amniotic fluid from patients with normal pregnancies and pregnancies complicated by fetal anencephaly or spina bifida.

METHODS

Amniotic fluid was obtained by amniocentesis during the first part of the second trimester from women under investigation for fetal neural tube defects or chromosomal abnormality. Samples were frozen soon after collection and stored at −30°C. The control patients were those who ultimately had an uncomplicated pregnancy and a normal infant; control amniotic fluid samples were matched as far as possible for gestational age and length of storage.

Glucose was determined by a glucose oxidase-peroxidase assay (Werner *et al*, 1970), protein by the Folin-Lowry method (Daughaday *et al*, 1952) and osmolality by the depression of freezing point (Johnson and Hoch, 1965). Sodium and potassium concentrations were measured on a Corning 450 flame photometer, and those of calcium (Trudeau and Freier, 1967) and magnesium (Hansen and Freier, 1967) were measured by atomic absorption spectrometry. Inorganic phosphate was determined by a phosphomolybdate assay (Gomorri, 1942).

The significance of differences between populations was assessed by Students 't' test using two-tailed tables.

RESULTS

The results are presented in Table I.

Concentrations of sodium, potassium and magnesium were similar in all of the groups. The mean amniotic fluid calcium concentration was higher by 35 per cent in spina bifida compared with anencephaly and this difference was significant ($p < 0\cdot 05$). Inorganic phosphate concentration in amniotic fluid (Fig. 1) was higher in fetal anencephaly than in both the control and fetal spina bifida patients ($p < 0\cdot 001$).

Amniotic fluid glucose concentrations (Fig. 2) were lower with fetal anencephaly than in controls and in patients with fetal spina bifida ($p < 0\cdot 001$), the highest amniotic fluid glucose value (6·89 mmol/l) was obtained in a patient with fetal anencephaly and being more than three standard deviations above the mean, this result was excluded from the statistical analysis. Two patients with anencephalic fetuses had repeat amniocenteses at intervals of one week. The two amniotic fluid glucose concentrations were 0·34 and 0·1 mmol/l for one patient and 0·17 and 1·19 mmol/l for the other patient.

The amniotic fluid protein levels (Fig. 3) were higher in patients with fetal anencephaly than in controls ($p < 0\cdot 005$) and in patients with fetal spina bifida ($p < 0\cdot 05$).

Amniotic fluid osmolality (Fig. 4) was higher with fetal spina bifida than in controls ($p < 0\cdot 025$) and in patients with an anencephalic fetus ($p < 0\cdot 05$). After the exclusion of two results outside three standard deviations of the mean, the respective significance of these differences increased to $p < 0\cdot 001$ and $p < 0\cdot 005$. In the two excluded samples there were corresponding abberant sodium concentrations.

To estimate the unaccounted contribution towards the osmolality, the sum of the sodium and the potassium concentrations were multiplied by 1·86 (Weissman and Pileggi, 1974), and the result was subtracted together with the glucose concentration from the amniotic fluid osmolality. These 'residual' contributions to osmolality were higher in amniotic fluid from pregnancies complicated by fetal spina bifida than in

TABLE I

Amniotic fluid composition

	Control (n = 16) Mean ± SD	Spina bifida (n = 11) Mean ± SD	Anencephaly (n = 20) Mean ± SD
Glucose (mmol/l)	2·72±0·57	2·28±0·43*	1·27±0·83****++++
Protein (g/l)	5·16±1·70	5·79±1·34	6·95±1·70***+
Sodium (mmol/l)	133·3±3·2	132·5±7·8	131·6±6·1
Potassium (mmol/l)	3·50±0·20	3·45±0·23	3·20±0·74
Calcium (mmol/l)	1·24±0·35	1·67±0·68	1·20±0·31+
Magnesium (mmol/l)	0·63±0·10	0·62±0·12	0·61±0·09
Phosphate (mmol/l)	0·86±0·13	0·73±0·19	1·13±0·28****++++
Osmolality (mosmol/kg)	264·9±5·8	275·0±12·7**	264·6±12·7+
Osmolar residuals (mosmol/kg)	8·0±5·3	19·9±6·4****	11·2±4·5++++
Gestational age (weeks)	17·4±1·8	18·6±3·4	18·7±1·8

* $p < 0\cdot 05$ ** $p < 0\cdot 025$ *** $p < 0\cdot 005$ **** $p < 0\cdot 001$ against controls (two tailed t-test)
+ $p < 0\cdot 05$ ++++ $p < 0\cdot 001$ against spina bifida (two tailed t-test)
Glucose concentrations in amniotic fluid associated with anencephaly were derived from 24 samples.

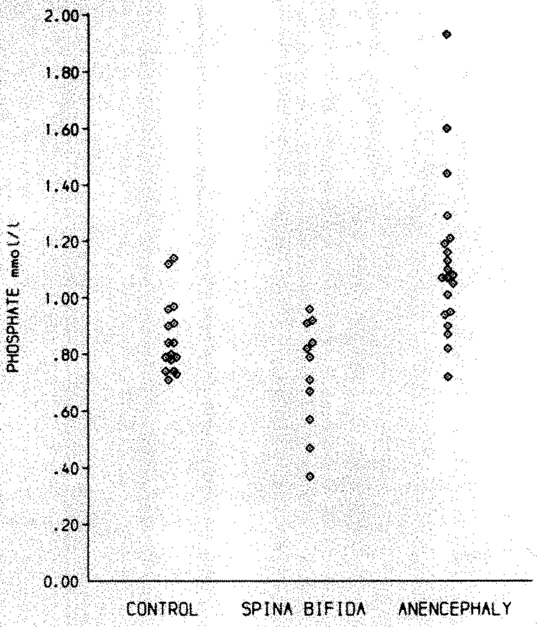

FIG. 1
Phosphate concentration in amniotic fluid.

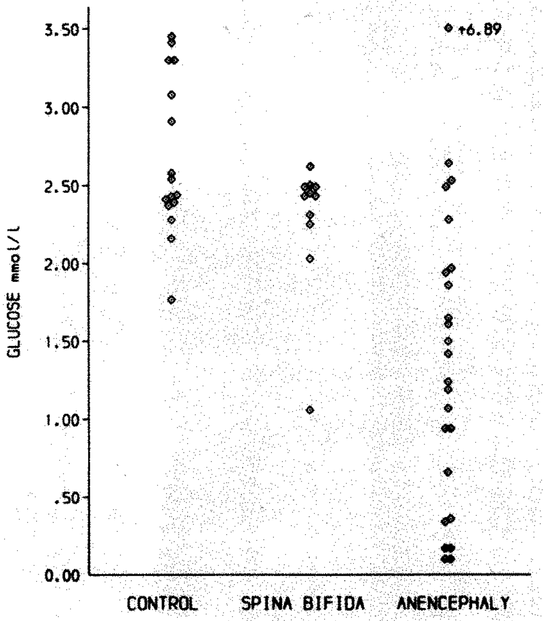

FIG. 3
Protein concentration in amniotic fluid.

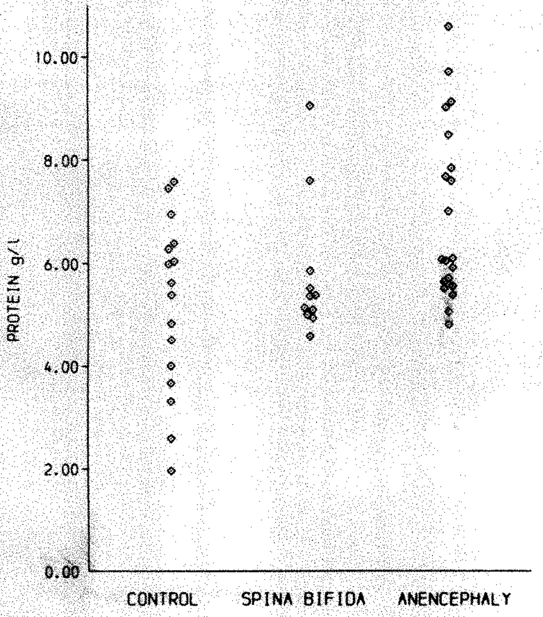

FIG. 2
Glucose concentration in amniotic fluid.

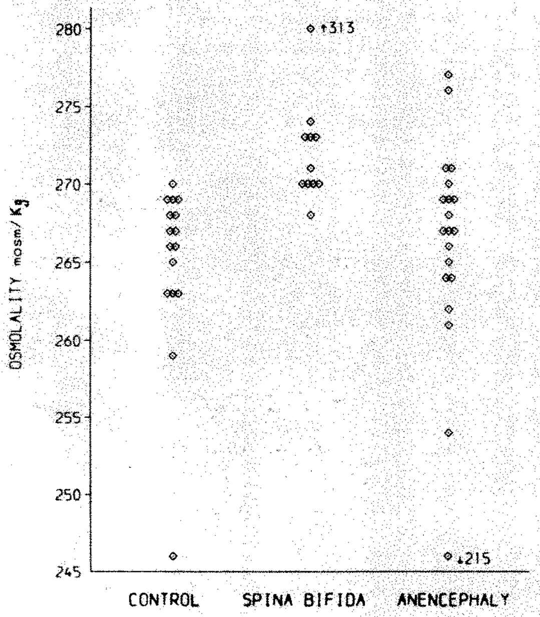

FIG. 4
Osmolality of amniotic fluid.

controls and in patients with pregnancies complicated by fetal anencephaly ($p < 0{\cdot}001$ and $p < 0{\cdot}001$ respectively).

DISCUSSION

The results obtained in control patients were similar to those previously reported (Benzie *et al*, 1974; Gillibrand, 1969; Sinha and Carlton, 1970). Previous studies have shown no appreciable variation in amniotic fluid composition over the range of gestational ages in this investigation. The small differences that would be expected from week to week in the first part of the second trimester would amount to less than one tenth of the standard deviation of the control range.

The elevated levels of amniotic fluid protein are probably due to the leakage of protein from the fetal circulation in the exposed tissue of the neural tube. The greater increase in amniotic fluid protein in anencephaly presumably results from the more extensive lesion. In anencephaly, alpha-fetoprotein can account for up to 0·2 mg/l and thus for only about 10 per cent of the rise in amniotic fluid total protein. The mean increase in amniotic fluid protein in anencephaly was about 35 per cent, and similar results have been found in patients studied during the third trimester of pregnancy (Brock and Nelson, 1974). Several protein components of amniotic fluid from pregnancies complicated by fetal anencephaly showed an increase of about 35 per cent. The bulk of the additional protein is thus due to a generalized increase.

Fetal calcium and phosphate metabolism differ substantially from the adult (Alexander *et al*, 1973). Thus, the increase in amniotic fluid calcium with fetal spina bifida and of phosphate with fetal anencephaly can not satisfactorily be explained in terms of the homeostatic mechanisms of the adult.

It is probable that the amniotic fluid glucose concentrations reflect fetal and not maternal levels. The wide range of glucose concentrations found in amniotic fluid from pregnancies complicated by fetal anencephaly, and the fluctuation evident from patients with fetal anencephaly who had repeat amniocenteses, might both be due to the absence of hypothalmic hormones resulting in the loss of glucose homeostasis and dysfunction of placental glucose transport.

Sodium and its counter ion account for most of the osmotic pressure. By calculating the contribution of these ions and of glucose to the osmolality of amniotic fluid we get an idea of the contribution by undetermined solutes. It can be seen that not only is the absolute osmolality higher in amniotic fluid from pregnancies complicated by fetal spina bifida but the amount attributable to unidentified solutes is 12 mosmol/kg more than in the controls. There may thus be chemical constitutents raised in spina bifida amniotic fluid which are unreported.

Although all of the parameters which we have measured showed considerable overlap, they may provide extra and welcome evidence about the presence or absence of a neural tube defect and perhaps even its precise nature.

ACKNOWLEDGEMENTS

We acknowledge the assistance of Prof K. M. Laurence and Dr I. Hughes (Welsh National School of Medicine, Cardiff) and Dr M. Kitau (St Bartholomew's Hospital, London) in providing some of the samples of amniotic fluid; we also thank Dr K. Blau for some useful discussion.

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PLACENTAL PROTEIN 5 IN FETAL AND MATERNAL COMPARTMENTS

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Summary

Placental protein 5 is produced by the syncytiotrophoblast and secreted into the maternal peripheral circulation reaching levels of approximately 30 μg per litre in normal pregnancy at term. In the present study the distribution of PP5 was examined in maternal and fetal compartments in 13 patients at delivery.

PLACENTAL protein 5 (PP5) is one of a new generation of recently identified proteins produced by the human syncytiotrophoblast (Bohn, 1972; Bohn and Winckler, 1977). PP5 has the electrophoretic mobility of a β_1 globulin, a molecular weight of 36 600 and a carbohydrate content of 19 per cent. The development of a specific and sensitive radioimmunoassay (RIA) for PP5 (Obiekwe *et al*, 1979) has permitted the measurement of circulating PP5 during pregnancy, hitherto not possible using immunodiffusion techniques (Bohn, 1972; Bohn and Winckler, 1977). Circulating PP5 levels rise gradually during pregnancy reaching a plateau of 32 μg/l at 36 weeks gestation (Obiekwe *et al*, 1979). In the present study we describe the distribution of PP5 in various maternal and fetal compartments.

METHODS

Maternal blood and urine, and amniotic fluid were collected from 13 patients immediately before vaginal delivery or Caesarean section. Umbilical artery and vein blood samples were collected immediately after delivery of the placenta. After separation of serum from blood, all samples were stored at —20°C until assayed as described previously (Obiekwe *et al*, 1979). Purified PP5 (Lot No. 49/48) and anti-PP5 antiserum (Lot No. 6060A) were kindly supplied by Dr H. Bohn, Behringwerke AG, Marburg. Some clinical characteristics of the patients are shown in Table I.

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TABLE I

Some clinical characteristics of 13 patients studied

Patient No.	Parity	Gestation (weeks)	Delivery	Infant sex	Baby weight (g)	Placental weight (g)
1	1	38	Vaginal	F	2850	750
2	2	40	Vaginal	F	3230	550
3	2	41	Vaginal	M	3720	750
4	1	38	Vaginal	M	2950	600
5	2	37	LSCS*	M	3100	650
6	2	40	LSCS	F	3490	550
7	2	40	Vaginal	F	3050	500
8	1	38	Vaginal	M	3300	600
9	2	39	Vaginal	M	4300	900
10	3	40	Vaginal	F	3500	450
11	1	39	LSCS	M	3850	650
12	2	40	Vaginal	M	3600	650
13	1	40	Vaginal	F	3450	500

* LSCS—Lower segment Caesarean section.

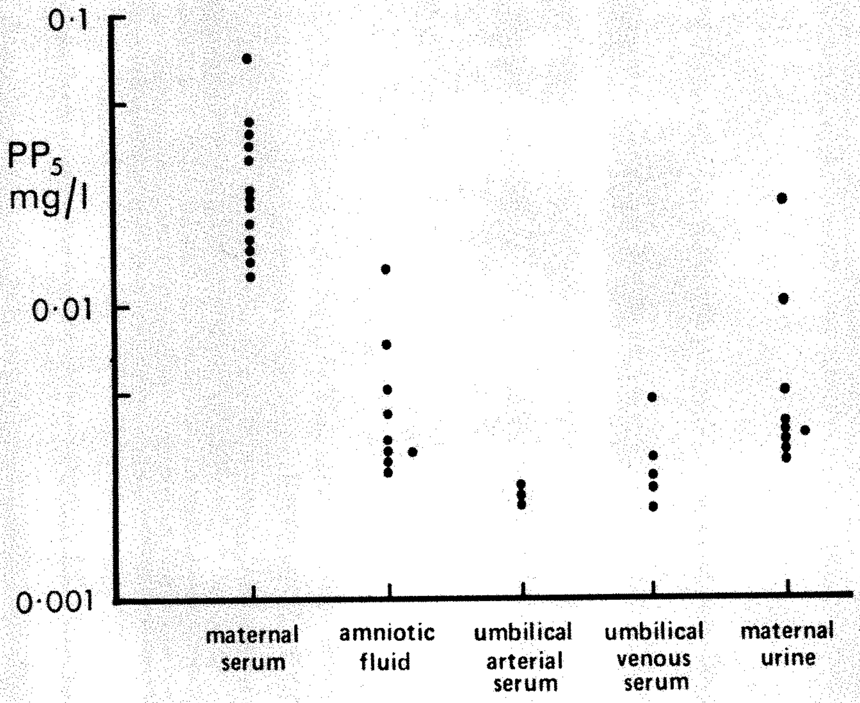

FIG. 1

Levels of PP5 in maternal and fetal compartments.

RESULTS

The concentrations of PP5 in the various fluids studied are shown in Figure 1. The highest levels were found in the maternal blood and there was no correlation between levels in this site and the other fluids examined. PP5 was detected in 9 of 13 amniotic fluids and 9 of 13 urine samples. Only 3 of 13 umbilical artery and 5 of 13 umbilical vein blood samples contained detectable PP5. PP5 levels in the various compartments were unrelated to mode of delivery, infant sex or weight, or placental weight.

DISCUSSION

The present study has demonstrated that in common with other placental proteins, PP5 is secreted selectively into the maternal compartment (Josimovich and McLaren, 1962; Kaplan and Grumbach, 1965; Berle, 1969; Grudzinskas *et al*, 1978). The levels in maternal blood are one order of magnitude greater than those in the fetal circulation which is similar to human placental lactogen (hPL) (Josimovich and McLaren, 1962; Kaplan and Grumbach, 1965) but contrasts with pregnancy specific β_1 glycoprotein in which levels are three orders of magnitude greater (Tatra *et al*, 1976; Grudzinskas *et al*, 1978).

The urinary concentration of PP5 is 10 per cent of the level in maternal blood which again is very similar to the findings with hPL. The failure to detect PP5 in some specimens of fetal blood was probably due to the sensitivity limit of the present assay technique. Insofar as the results can be interpreted, there was no consistent arteriovenous difference in the umbilical circulation.

The levels of PP5 in amniotic fluid were higher than those in the fetus; the source of amniotic fluid PP5 is not certain, but information on other placental proteins suggests the maternal circulation is likely to be the principal source (Niven *et al*, 1974; Grudzinskas *et al*, 1978).

The function of PP5 is unknown; however, the fact that PP5 levels are strikingly higher in serum than in plasma (Obiekwe *et al*, 1979) suggests that it may be related to the coagulation mechanism, and perhaps plays some role in maintaining blood flow within the intervillous space.

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INDOMETHACIN IN THE TREATMENT OF PRIMARY DYSMENORRHOEA

BY

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Summary

Thirty-two patients were treated with placebo tablets or indomethacin (25 mg three times daily) in a six-month, double-blind, cross-over trial. During indomethacin therapy, 75 per cent of patients experienced significant pain relief while associated vomiting and diarrhoea were relieved in 44 per cent and 64 per cent of patients respectively. The efficacy of indomethacin was comparable to that of other prostaglandin synthetase inhibitors.

THE prostaglandin E (PGE) and PGF content of the endometrium has been found to increase markedly during the late luteal phase of the cycle (Downie *et al*, 1974) and dysmenorrhoeic women were found to have more PGF in their menstrual blood than normal patients (Pickles *et al*, 1965). Prostaglandins may thus play a role in causing the pain of primary dysmenorrhoea and the often associated vomiting and diarrhoea (Downie *et al*, 1974). This idea is supported by the finding that indomethacin (Christensen, 1974) and flufenamic acid (Schwartz *et al*, 1974) both had a beneficial effect on patients with primary dysmenorrhoea but neither of these studies was placebo-controlled. More recently double-blind placebo-controlled studies of naproxen sodium (Henzl *et al*, 1977) and flufenamic acid (Kapadia and Elder, 1978) have shown that these prostaglandin synthetase inhibitors are of significant benefit. An open comparative study showed that mefenamic acid was slightly better than flufenamic acid or naproxen (Anderson *et al*, 1978). We now describe the use of indomethacin in a double-blind, placebo-controlled, cross-over study.

PATIENTS AND METHODS

Thirty-eight patients aged between 12 and 41 years who had given informed consent entered the trial; six dropped out leaving 32. Patients with a history of dyspepsia, with pelvic abnormality or on combined oral contraceptives were not allowed to enter the study. Allocation to either the indomethacin or placebo group for the first three months of treatment was random. The placebo tablets were identical to those containing the active drug and neither patient nor doctor was aware of which preparation was being taken. After three cycles patients were changed to the alternative preparation which was taken for a further three cycles. One tablet was taken three times a day with meals, starting as soon as menstrual bleeding was noticed and continuing for as long as the patient thought necessary. Patients were seen monthly when points were alloted for pain relief as follows: none (0), slight (1), moderate (2), complete (3).

The number of episodes of diarrhoea or

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vomiting occurring during each menstrual period was recorded. The statistical significance of the difference between the mean scores for both three month trial periods was assessed by Students 't' test.

RESULTS

Details of the 32 patients studied are shown in Table I. Seventy-five per cent of patients experience significant relief of their pain. The number of episodes of diarrhoea and vomiting were significantly reduced in 43·8 per cent and 63·9 per cent of patients who suffered from these symptoms. Significant pain relief was defined as an improvement in the total three-monthly score of three or more points, or the total abolition of pain. A reduction by a number of three or more in the monthly episodes of vomiting or diarrhoea was regarded as a significant improvement. The relief of symptoms

TABLE I

Data on patients before treatment

Primiparous patients	30 (94 per cent)
Multiparous patients	2 (6 per cent)
Age (years) Mean ± SD	24·0±8·5
Duration of dysmenorrhoea (years) Mean ± SD	9·5±8·2
Patients with nausea	19 (59·3 per cent)
Patients with vomiting	11 (34·4 per cent)
Patients with diarrhoea	16 (50·0 per cent)

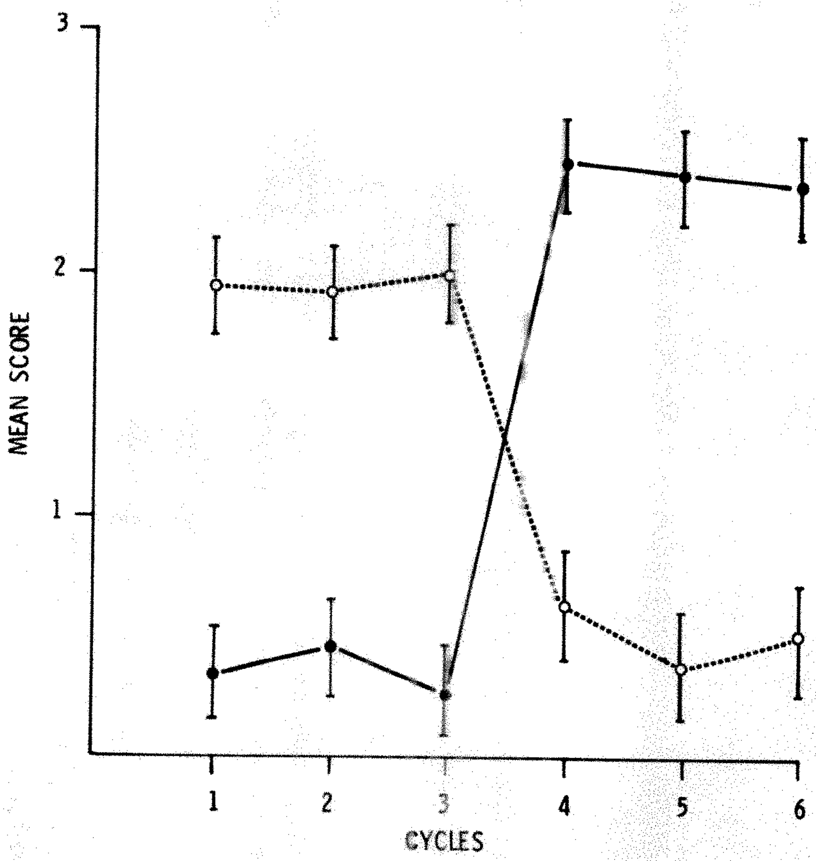

FIG. 1

Mean score of pain relief during each menstrual cycle for group of patients being treated first with placebo followed by indomethacin (●———●), or with indomethacin followed by placebo (○ - - - - ○)

TABLE II

Relief of pain, vomiting and diarrhoea

	Treatment		Significance of difference between means
	Placebo	Indomethacin	
Score for pain relief (32 patients) Mean ± SD	1·6±2·2	6·2±3·3	p <0·001
No. of episodes of vomiting per month (16 patients) Mean ± SD	3·0±2·7	1·1±1·7	p <0·025
No. of episodes of diarrhoea per month (11 patients) Mean ± SD	3·8±3·1	1·9±2·6	n.s.

assessed by the difference between the mean scores of the two three-monthly treatment periods are shown in Table II. The degree of pain relief according to whether the placebo or active drug was administered first is shown in Figure 1. Six patients (18·6 per cent) had significant side-effects attributable to indomethacin: three patients had dizziness, two had nausea and one had both.

COMMENTS

The reduction in plasma concentrations of $PGF_{2\alpha}$ and 13,14 dihydro, 15-keto $PGF_{2\alpha}$ after treatment with oral indomethacin, with the simultaneous reduction of uterine tone and relief of symptoms strongly suggests that prostaglandins are involved in the aetiology of primary dysmenorrhoea (Lundström *et al*, 1976). The relief of pain and vomiting brought about by indomethacin in this study was significantly better than the placebo but the relief of diarrhoea was not so marked. The results confirm that indomethacin is one of the drugs which can be used in the treatment of primary spasmodic dysmenorrhoea but the incidence of drug related side-effects may be higher than with the fenamates.

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SERUM GONADOTROPHINS, PROLACTIN AND OVARIAN STEROIDS IN PRIMARY DYSMENORRHOEA

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Summary

Serum samples were collected from 27 women with incapacitating primary dysmenorrhoea and from 16 normal women in the early part of the cycle (between days 3 to 6), at midcycle (between days 13 to 16) and in the late part of the cycle (between days 23 to 26) for determination of FSH, LH, prolactin (PRL), 17β-oestradiol (E_2) and progesterone (P). The gonadotrophin and P levels showed normal and similar ovulatory patterns in both groups. The PRL concentrations (mean±SD) in dysmenorrhoeic women were lower than normal in the early part ($9\cdot2\pm4\cdot0$ ng/ml *vs* $14\cdot5\pm7\cdot3$ ng/ml, $p<0\cdot01$) and in late part of the cycle ($11\cdot7\pm5\cdot2$ ng/ml *vs* $16\cdot5\pm10\cdot2$ ng/ml, $p<0\cdot05$), but not so at midcycle ($9\cdot1\pm2\cdot8$ ng/ml *vs* $10\cdot4\pm4\cdot4$ ng/ml, $p>0\cdot05$). The E_2 level was higher than normal in dysmenorrhoeic women in the late cycle ($163\cdot0\pm76\cdot7$ pg/ml *vs* $93\cdot3\pm64\cdot3$ pg/ml, $p<0\cdot01$), but apart from this the ratio of E_2/P did not differ between the groups. These hormonal changes may be related to an excessive production of endometrial prostaglandins in primary dysmenorrhoea.

BOTH prostaglandin (PG) E_2 and $PGF_{2\alpha}$ are present in the human endometrium and show cyclic variation in their concentration with peak levels during the secretory phase (Downie *et al*, 1974; Green and Hagenfeldt, 1975; Jordan and Pokoly, 1977; Pickles *et al*, 1965; Singh *et al*, 1975; William *et al*, 1976). Their excessive release at the onset of menstruation is probably responsible for the pain of primary dysmenorrhoea (Pickles, 1957; Pickles *et al*, 1965; Ylikorkala and Dawood, 1978). It is conceivable that the final reason for primary dysmenorrhoea is to be found among the ovarian steroids which seem to regulate the synthesis of endometrial PGs *in vivo* (Downie *et al*, 1974; Green and Hagenfeldt, 1975; Pickles *et al*, 1965; Singh *et al*, 1975; William *et al*, 1976) and *in vitro* (Cane and Vilke, 1975). Previously, it has been claimed that urinary excretions of oestrogens and pregnanetriol are lower than normal in patients with dysmenorrhoea (Bell and Loraine, 1966). In this study we compared the pituitary-ovarian function in women with and without primary dysmenorrhoea by measuring serum levels of gonadotrophins, prolactin and ovarian steroids in different phases of the menstrual cycle.

SUBJECTS AND METHODS

Twenty-seven women with severe primary dysmenorrhoea of 4 to 9 years' duration and 16 comparable women without dysmenorrhoea were studied (Table I).

TABLE I

Clinical data on the women studied

	Patients with dysmenorrhoea (n = 27) Mean ± SD	Patients without dysmenorrhoea (n = 16) Mean ± SD
Age (years)	20·1 ± 2·1	21·5 ± 2·4
Menarche (years)	12·8 ± 1·3	12·6 ± 0·9
Length of menstrual cycle (days)	28·6 ± 1·9	28·8 ± 1·5
Duration of menstrual bleeding (days)	4·9 ± 1·2	4·7 ± 0·7
Day of cycle for blood sampling		
early cycle	4·9 ± 1·2	4·3 ± 1·2
midcycle	13·8 ± 0·8	13·5 ± 0·3
late cycle	24·7 ± 1·2	24·5 ± 0·9

Blood samples were collected during the early part of the cycle (between days 3 to 6), at midcycle (between days 13 to 16) and in the late part of the cycle (between days 23 to 26). All three samples were obtained from 16 dysmenorrhoeic women and from 12 control women while only one blood sample was collected at the appropriate time of the menstrual cycle from the others. The mean cycle days at sampling were similar in both groups (Table I). The menstrual period after the study cycle was painful in all women included in the dysmenorrhoea group and painless in the control women.

Serum was separated with centrifugation and stored at —20°C until assayed. Estimations of serum follicle stimulating hormone (FSH), luteinising hormone (LH) and prolactin (PRL) were made using CEA-IRE-SORIN radioimmunoassay kits (Department des Radio-elements, B.P. No 21, 91190 Gif-sur-Yvette, France), and the details of the assays have been given elsewhere (Hammond *et al*, 1977*a*). Levels of 17β-oestradiol (E_2) and progesterone (P) were also measured with radioimmunoassays using iodinated ligands (Hammond *et al*, 1977*b*). The measurements of each hormone were done in duplicate, and all the samples for each hormone determination were included in the same batch. The within assay variation was 7·2 per cent in peptide hormone assays and 10·8 per cent in steroid hormone assays.

Student's 't' test was employed for the statistical comparisons between groups.

RESULTS

The FSH and LH levels showed normal patterns during the menstrual cycle and were similar in both groups (Fig. 1, Table II). In one woman with dysmenorrhoea and in another without, an LH peak was observed.

The PRL level ranged from 2·0 to 25·2 ng/ml in the dysmenorrhoea group and from 4·2 to 32·3 ng/ml in the control group (Fig. 1). In the early and late phases of the menstrual cycle the mean PRL level was lower in the dysmenorrhoea group than in the control group (Table II). Since the PRL level does not change to any great extent during the menstrual cycle, the mean of all PRL values was calculated; it was also lower ($p < 0·01$) in dysmenorrhoeic women (10·1 ± 4·3 ng/ml) than in the control women (13·4 ± 7·7 ng/ml).

The E_2 level showed a normal pattern in the course of the menstrual cycle in both groups (Fig. 2). In the late part of the cycle, the E_2 level in women with dysmenorrhoea (163·0 ± 76·7 pg/ml) was higher ($p < 0·01$) than that in the control women (93·3 ± 64·3 pg/ml) whereas on other cycle days, the mean E_2 levels did not differ between the groups (Table II). All women showed an ovulatory P level late in the cycle (Fig. 2). One woman in the control group had a P level of only 1·5 ng/ml on the 24th cycle day, but the cycle was regarded ovulatory, as the P level had risen significantly. The mean P concentration did not differ between the groups (Table II).

TABLE II

Levels of FSH, LH, prolactin (PRL), 17-β-oestradiol (E_2) and progesterone (P) in women with dysmenorrhoea and in controls in different phases of the menstrual cycle

Cycle days	FSH (mIU/ml) Mean ± SD		LH (mIU/ml) Mean ± SD		PRL (ng/ml) Mean ± SD		E_2 (pg/ml) Mean ± SD		P (ng/ml) Mean ± SD	
	Dysmenorrhoea	Control	Dysmenorrhoea	Control	Dysmenorrhoea	Control	Dysmenorrhoea	Control	Dysmenorrhoea	Control
					**					
3–6	6·3±1·5	5·5±1·3	12·6± 9·2	13·1± 7·8	9·2±4·0	14·5±7·3	34·2± 12·7	49·9± 34·7	0·04±0·13	0·17±0·14
13–15	13·1±20·0	5·8±5·0	34·8±34·2	23·6±34·0	9·1±2·8	10·0±4·4	142·6±116·4	151·4±115·7	1·31±2·0	0·69±0·99
					*		**			
23–26	4·0±3·6	3·2±1·5	13·9±18·6	10·6±4·2	11·7±5·2	16·5±10·2	163·0± 76·7	93·9± 64·3	11·4±3·3	9·5±7·0

* = $p < 0{\cdot}05$ and ** = $p < 0{\cdot}01$ indicate the significances in comparison between the groups.

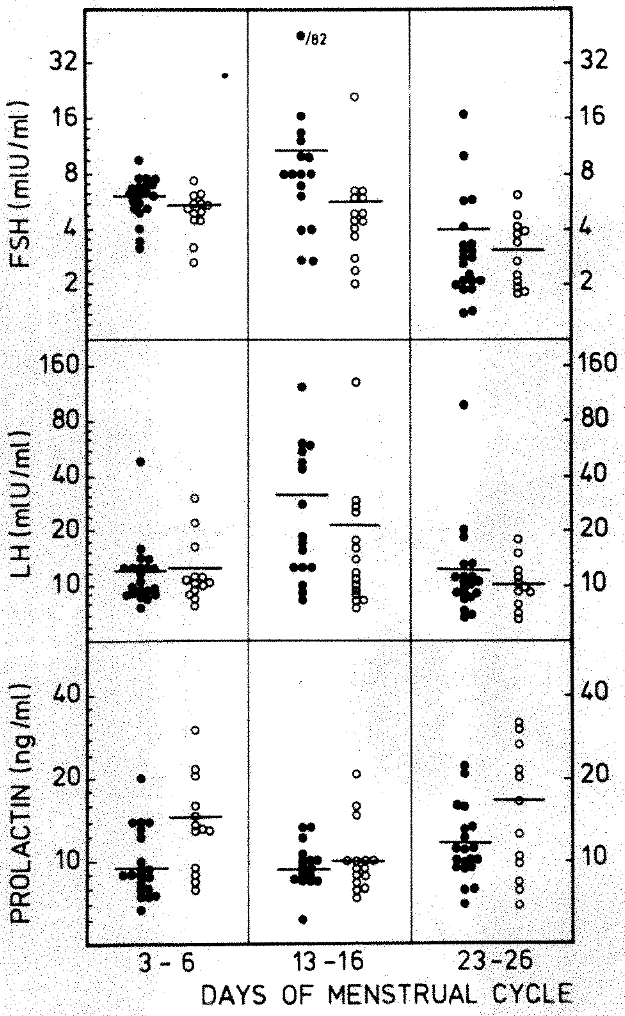

FIG. 1

Serum levels of FSH, LH and prolactin in different phases of the dysmenorrhoeic (●) or nondysmenorrhoeic (○) menstrual cycle. The horizontal lines indicate the mean levels of each hormone. Note the logarithmic scale.

The ratio of E_2/P ranged from 7·6 to 38·5 in patients with dysmenorrhoea and from 6·3 to 34·0 in the control women in the late part of the cycle. The mean ratio was equal in both groups, $17{\cdot}8 \pm 12{\cdot}1$ in patients with dysmenorrhoea and $14{\cdot}7 \pm 8{\cdot}8$ in the control group ($p > 0{\cdot}05$).

DISCUSSION

This study suggests that the pituitary-ovarian function differs between the painless and pain-affected menstrual cycles. The PRL concentration is lower and the E_2 concentration is higher in dysmenorrhoeic than non-dysmenorrhoeic women. The high E_2 level may cause the excessive production of endometrial PGs. This is supported by a positive correlation between endometrial PGF concentrations and uterine venous E_2 levels (Jordan and Pokoly, 1977) and between ovarian venous oestrogens and $PGF_{2\alpha}$ levels in women (Sezer *et al*, 1977). Support for

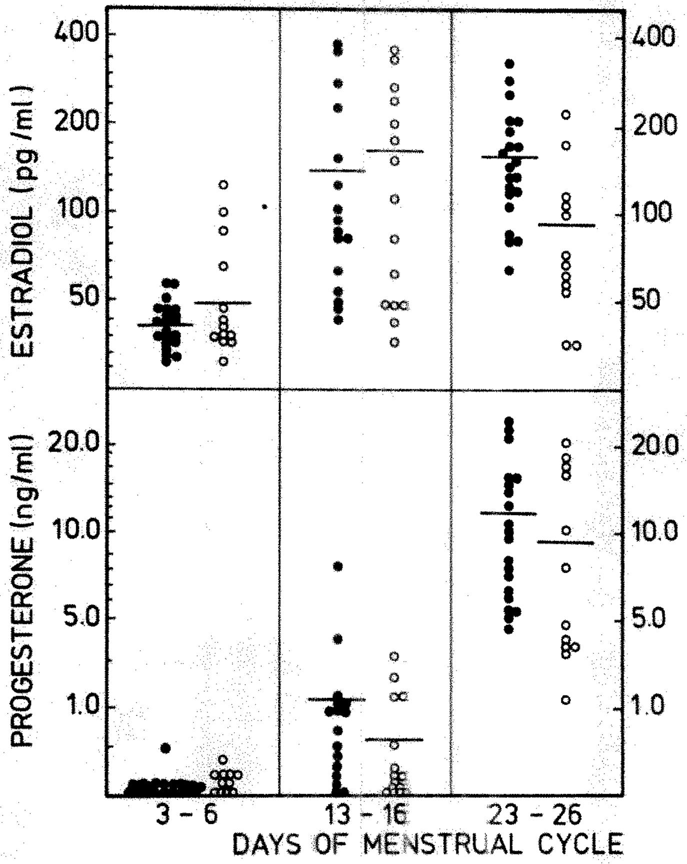

FIG. 2

Serum levels of 17β-oestradiol (E_2) and progesterone (P) in different phases of the dysmenorrhoeic (●) or nondysmenorrhoeic (○) menstrual cycle. The horizontal lines indicate the mean levels of each hormone. Note the logarithmic scale.

this theory also comes from reports of an increased PG production by human endometrium (Cane and Vilke, 1975) or by guinea pig uterus *in vitro* after oestradiol treatment (Naylor and Poyser, 1975; Wlodawer *et al*, 1976).

Like Hwang *et al* (1971) and McNeilly and Chard (1977), we observed no apparent relation between levels of PRL and those of E_2 or P during the menstrual cycle. It is, however, known that patients with ovulatory infertility have significantly higher proliferative phase serum PRL levels than fertile controls although hyperprolactinemia was uncommon (Lenton *et al*, 1977). The PRL concentration may thus be more 'optimal' and apparently lower in some women than in others already in the early part of the menstrual cycle when the follicle is growing. The lower PRL concentration may result in the development of a more mature follicle and hence in the longer duration of the oestrogen elevation. Thus the low PRL level could be a primary change in primary dysmenorrhoea. It is however difficult to explain why PRL levels were low before menstruation in the presence of high E_2 concentration, because oestrogens stimulate PRL secretion. Perhaps other factors including P (Rakoff and Yen, 1978) are also of significance in the control of PRL release.

Postovulatory progesterone is apparently necessary for PG synthesis *in vivo* and thus for dysmenorrhoea, since dysmenorrhoea occurs only in ovulatory cycles (Wilson and Kurzrok, 1938). It is also known that exogenous P administered to ewes increases the endometrial content of $PGF_{2\alpha}$ (Wilson *et al*, 1972). In our study P levels were similar in painful and painless menstrual cycles. Therefore the excessive endometrial production of PGs in dysmenorrhoea might be more related to the relatively high E_2 than to the P concentration at the onset of bleeding.

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IMMEDIATE POSTPARTUM INSERTION OF A COPPER-WIRED INTRAUTERINE CONTRACEPTIVE DEVICE, THE MLCu250

BY

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Summary

The MLCu250, a copper-wired intrauterine contraceptive device, was inserted in 600 women immediately after delivery of the placenta. Thirty months after insertion, 9843 woman months of experience were computerized and the data analysed according to the life-table method. The gross cumulative pregnancy and expulsion rates were 1·3 and 6·0 respectively. No serious complications were observed and the puerperium was uncomplicated.

The advantage of inserting an intrauterine contraceptive device (IUCD) immediately after the delivery of the placenta are obvious. Unfortunately high expulsion rates have been reported (Banharnsupawat and Rosenfield, 1971; Zatuchni, 1970; Apelo *et al*, 1976; P. Rowe, 1978, personal communication) and many investigators fear uterine perforation, endometritis, protracted bleeding, and delayed uterine involution as a result of the postpartum IUCD.

In the course of a multicentre trial of a new copper-wired IUCD, the MLCu250 (Fig. 1) (Thiery *et al*, 1978*a*), we found a low expulsion rate and therefore decided to try fitting the MLCu250 immediately post partum. Preliminary results were encouraging (Thiery *et al*, 1978*b*) and the present report summarizes our experience over 30 months.

PATIENTS AND METHODS

All patients were women requesting an IUCD and lacking contraindications to its use.

All IUCDs were inserted by consultants or registrars immediately after delivery of the placenta and inspection of the cervix and vagina, and before episiotomy repair. A detailed description of the technique of IUCD insertion has been given elsewhere (van Os *et al*, 1976). The two most important points are application of one or more sponge forceps to the anterior lip of the cervix and the use of bimanual palpation to ensure correct fundal placement of the IUCD. Five to six weeks after the delivery patients were reviewed and the polyethylene threads were trimmed. If the threads could not be seen, gentle attempts were made to extract them from the cervical canal with a platinum loop or a blunt-ended suction catheter. If these manoeuvres failed, the patient was re-examined after her first menstrual period; if the threads were still not seen, an X-ray was taken with an Allis forceps clamped on the anterior lip of the cervix. The IUCD was only removed if inversion of the device within the uterine cavity was de-

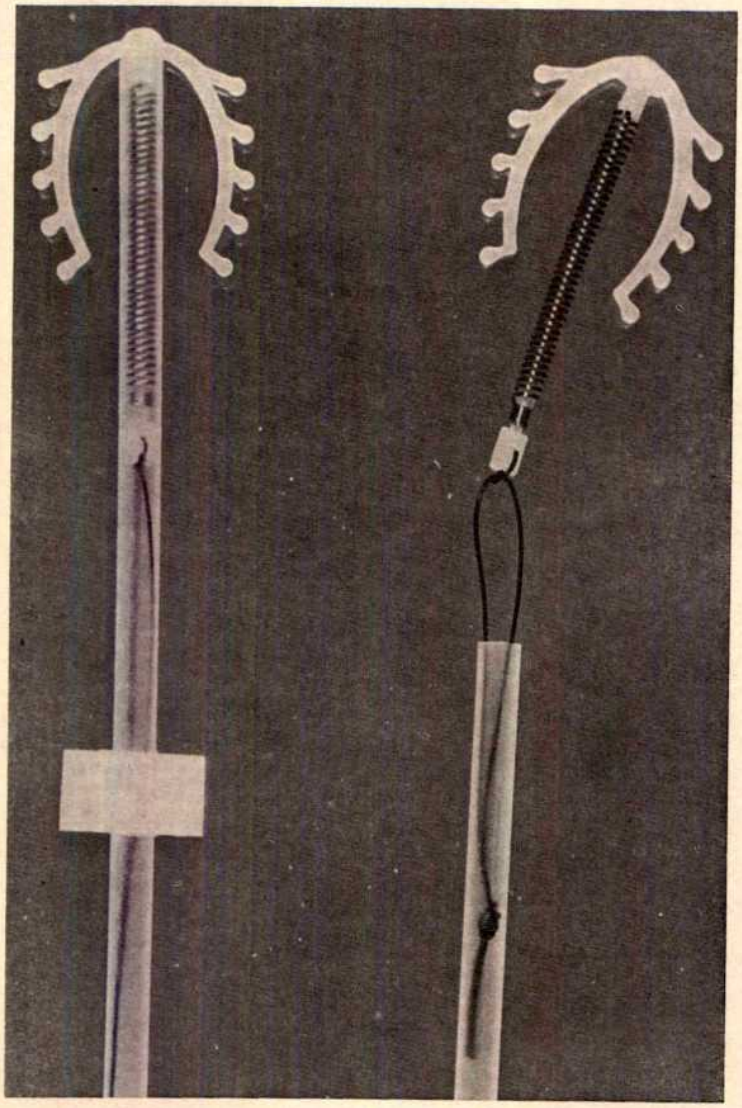

FIG. 1

The MLCu250 within (left) and removed from (right) the inserter tube.

tected; a new IUCD was then inserted immediately.

Between October 1, 1975 and April 31, 1978 a total of 600 IUCDs were inserted immediately after delivery of the placenta. The present report concerns the observations made up to August 1, 1978, and covers a total of 9843 woman months. Event rates were calculated by life-table analysis with a computer programme (Tietze and Lewit, 1973) on an IBM 370/148-OS/VS1.

RESULTS

The gross cumulative event rates per 100 users at six-months intervals during the first 30 months of use are given in Table I. At one year, the expulsion rate amounted to 5·8 and it did not increase significantly thereafter.

The possible effects of age and parity were analysed for periods up to 2 years (Tables II and III). The removal rate for bleeding and/or pain suggested an inverse relationship with the

TABLE I

Immediate postpartum insertion of the MLCu250. Gross cumulative event rates per 100 users at six month intervals

	Time interval (months)				
	6	12	18	24	30
Number enrolled	600	—	—	—	—
Woman months of use	3315	5895	7770	9138	9843
Events					
unplanned pregnancy	0·6(0·1–1·7)	1·0(0·3–2·3)	1·3(0·5–2·8)	1·3(0·5–2·8)	1·3(0·5–2·8)
expulsions	3·7(2·1–5·2)	5·8(3·8–7·8)	6·0(4·0–8·1)	6·0(4·0–8·1)	6·0(4·0–8·1)
removals					
—bleeding/pain	4·3(2·4–5·5)	7·1(4·5–9·8)	9·1(5·7–11·9)	10·7(6·3–13·2)	11·8(7·2–14·8)
—desire for further pregnancy	0·6(0·1–1·6)	7·3(4·8–9·8)	12·8(9·5–16·1)	15·9(12·2–19·7)	18·0(14·0–22·1)
—other personal reasons	3·6(2·0–5·1)	5·1(3·2–7·0)	6·0(3·9–8·0)	6·4(4·2–8·7)	7·1(4·7–10·0)
—doctor's recommendation	1·6(0·7–3·0)	1·6(0·7–3·0)	1·9(0·9–3·5)	1·9(0·9–3·5)	1·9(0·9–3·5)
Continuation rate	87·2	72·7	64·0	59·7	55·8
Lost to follow-up	1·5(0·6–2·9)	4·5(2·6–6·3)	5·9(3·7–8·0)	11·4(8·0–14·8)	15·0(11·0–19·1)
Released from study	0·4(0·0–1·3)	0·6(0·1–1·8)	0·9(0·2–2·3)	1·3(0·4–3·0)	1·3(0·4–3·0)

Values in parentheses give upper and lower confidence limits at 95 per cent level.

TABLE II

Immediate postpartum insertion of the MLCu250. Gross cumulative event rates per 100 users at 12 and 24 months, according to age

	12 months		24 months	
	<31 years	>30 years	<31 years	>30 years
Number enrolled	447	153	447	153
Woman months of use	4407	1488	6776	2362
Events				
unplanned pregnancy	1·3(0·4–3·1)	0·0(0·0–2·8)	1·3(0·4–3·1)	1·1(0·0–6·3)
expulsions	6·0(3·6–8·3)	5·1(2·1–10·6)	6·0(3·6–8·3)	6·2(2·7–12·1)
removals				
—bleeding/pain	8·2(4·0–10·7)	7·7(3·2–13·9)	11·7(6·4–15·0)	7·7(3·2–13·9)
—desire for further pregnancy	7·4(4·5–10·3)	7·0(3·1–13·8)	10·3(12·0–20·1)	14·8(7·8–22·0)
—other personal reasons	4·6(2·5–6·7)	6·6(3·0–12·4)	5·7(3·2–8·1)	8·7(3·7–13·7)
—doctor's recommendation	1·0(0·3–2·5)	3·4(1·1–8·0)	1·4(0·5–3·2)	3·4(1·1–8·0)
Continuation rate	73·5	73·6	65·0	62·5
Lost to follow-up	4·3(2·2–6·3)	5·0(1·9–11·0)	12·1(8·1–16·2)	9·5(4·4–18·0)
Released from study	0·8(0·2–2·4)	0·0(0·0–2·8)	1·2(0·3–3·1)	1·4(0·0–7·8)

Values in parentheses give upper and lower confidence limits at 95 per cent level.

TABLE III

Immediate postpartum insertion of the MLCu250. Gross cumulative event rates per 100 users at 12 and 24 months, according to parity

	12 months			24 months		
	Parity			Parity		
	1	2	more than 2	1	2	more than 2
Number enrolled	295	201	301	295	201	301
Woman months of use	2839	1992	3013	4245	3205	4828
Events						
unplanned pregnancy	0·9(0·1–3·1)	1·1(0·1–4·1)	1·2(0·2–3·4)	0·9(0·1–3·1)	1·1(0·1–4·1)	1·7(0·5–4·3)
expulsions	6·4(3·4–9·4)	5·7(2·7–10·5)	5·3(2·5–8·0)	6·3(3·4–9·4)	5·7(2·7–10·5)	5·7(2·9–8·6)
removals						
—bleeding/pain	8·6(4·0–12·0)	8·9(2·8–12·7)	7·7(3·2–10·7)	9·6(4·3–13·2)	14·0(5·7–19·9)	11·7(5·7–15·5)
—desire for further pregnancy	11·3(5·9–15·6)	3·4(1·1–7·8)	3·6(2·8–8·5)	27·0(20·4–33·6)	5·1(2·0–10·4)	5·7(2·5–10·5)
—other personal reasons	4·5(2·0–7·1)	5·8(2·8–10·5)	5·7(2·8–8·5)	5·7(2·6–8·8)	6·6(2·8–10·5)	7·3(4·0–10·5)
—doctor's recommendation	0·4(0·0–2·2)	3·2(1·2–6·9)	2·8(1·2–5·5)	0·4(0·0–2·2)	4·0(1·6–8·2)	3·4(1·5–6·3)
Continuation rate	68·3	75·1	76·5	50·5	67·5	67·9
Lost to follow-up	4·0(1·9–7·4)	4·9(2·1–9·5)	4·5(1·8–7·1)	16·0(9·9–22·0)	7·7(3·2–12·1)	7·9(4·1–11·7)
Released from study	1·30(0·3–3·7)	0·0	0·0	1·9(0·5–4·9)	0·0	0·0

Values in parentheses give upper and lower confidence limits at 95 per cent level.

TABLE IV

Immediate postpartum insertion of the MLCu250. Unplanned pregnancies

Patient No.	Age	Gravidity–parity	Number of previous IUCD insertions	Position of IUCD	Interval from insertion to onset of last period (months)	Time of IUCD removal (in weeks of amenorrhea)
1	26	1–1	none	in situ	4	8
2	19	1–1	none	in situ	4	7
3	27	1–1	one	in situ	8	6
4	33	4–4	none	partially expelled	15	9
5	29	5–5	none	partially expelled*	8	6
6	28	1–1	none	in situ	9	7

Note: * Undiagnosed inversion within the uterine cavity. All pregnancies were normal and all babies healthy.

woman's age. Parity did not have an important effect on event rates, but the removal rate because of bleeding and/or pain was slightly higher in patients who had had more than two confinements.

During the period covered by the investigation, six unplanned pregnancies occurred, all of them within the first year, but there were no ectopic pregnancies (Table IV).

DISCUSSION

The MLCu250 has proved a good IUCD for immediate postpartum use. Effectiveness and continuation rate were fair, and serious complications did not occur. We believe that inversion of the device within the uterine cavity could lead to penetration into and ultimately to perforation of the uterine fundus by the stem of the MLCu250. Thus we believe that attempts should be made to diagnose inversion of the device within the uterine cavity and that the IUCD should be removed if inversion is present.

Immediate postpartum insertion of the MLCu250 is easy. Only in five instances was it difficult to negotiate the isthmic region; in these patients the IUCD was withdrawn and a new one inserted. Some authors associate spontaneous expulsion with poor placement of the device and advocate the use of a longer inserter tube (P. Rowe, 1978, personal communication). We had no trouble with the regular MLCu250 inserter (length 20 cm, outer diameter 0·35 cm) and our expulsion rate suggests correct placement in the majority of instances. In about 20 women a 42 cm inserter tube has been tried, but was found to be too cumbersome.

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THE EFFECT OF LAPAROSCOPIC STERILISATION BY DIATHERMY OR SILASTIC BANDS ON POST-OPERATIVE PAIN, MENSTRUAL SYMPTOMS AND SEXUALITY

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Summary

A total of 530 patients was reviewed six months after laparoscopic sterilisation by diathermy (235 patients) or silastic bands (295 patients). In the immediate post-operative period severe lower abdominal pain was more common in the patients who had silastic bands. There was one failure with diathermy and two with silastic bands. There were no differences in the nature or incidence of menstrual problems when the two methods were compared. In all, 40 per cent of patients reported an increase in menstrual blood loss and 26 per cent of patients an increase in menstrual pain, and this could not be attributed entirely to stopping oral contraception; 42 per cent of patients reported improvement in their sex lives after sterilisation, while 6·6 per cent reported deterioration mainly due to lack of libido. There was some regret about the operation in 5·1 per cent of patients.

THE physical and psychological sequelae of sterilisation remain a matter of controversy. This is probably because most reports of undesirable sequelae have been retrospective (Leading Article, 1976) and authors have been denied the advantage of studying a defined population.

Neil *et al* (1975) reported an increased incidence of menstrual problems after laparoscopic tubal diathermy, and Chamberlain and Foulkes (1976) found that about one-third of patients had longer and heavier periods after diathermy. Lieberman *et al* (1978) reported that laparoscopic sterilisation with a spring-loaded clip did not adversely affect menstrual patterns.

In this study we attempted to review 566 consecutive patients who were sterilised either by laparoscopic tubal diathermy or by laparoscopic application of silastic bands, with particular reference to menstrual and sexual problems at six months after operation.

METHOD

We attempted to review 566 women six months after sterilisation. All patients (except those sterilised at the time of therapeutic abortion) who had been sterilised by laparoscopic tubal diathermy or by laparoscopic application of silastic bands after April, 1976, and more than six months before the survey, were recruited into the study. A questionnaire was completed during an interview in the clinic of 377 of the 566 patients. The remaining 189 patients who could not or did not wish to attend the clinic were sent a questionnaire with a letter explaining the purpose of the study, and 126 questionnaires were returned (including eight marked gone away). Thirty-five of the remaining 63 patients completed the questionnaire in response to a further hand-written note asking for their co-operation. Thus, we had completed questionnaires from 530 patients making a follow-up rate of 93·6 per cent.

Of these 530 patients, 235 had been sterilised by diathermy and 295 by silastic bands. The failures (see Results) were excluded from the analysis of the menstrual and sexual problems data. Many of the patients (170 sterilised by diathermy and 161 sterilised by silastic bands) had been reviewed at two weeks as part of an earlier study (Templeton *et al*, 1977, Lawson, 1977, unpublished data).

RESULTS

The mean age of the patients was 34·1 years, and the mean parity was 2·3. Details are given in Figures 1 and 2. The social class distribution of the women, based on the husband's occupation, was not significantly different from the Edinburgh City population based on the 1971 census.

The contraceptive practice of the patients at the time of sterilisation was as follows: 55 per cent used oral contraception, 10 per cent had an intrauterine contraceptive device (IUCD), 20 per cent used barrier methods, and 15 per cent said they were not using any contraception.

Failures and abdominal pain

At six months there had been two failures in the silastic band group and one in the diathermy group. The failures in the silastic band group were both due to misapplication of the ring on one side (ovarian ligament and mesosalpinx respectively). The diathermy failure was due either to inadequate destruction of the tube, or conception just before operation.

In the diathermy group, three patients complained of continuing lower abdominal pain at six months and a further two had been treated for pelvic infection. One of these patients had been confined to bed for a month. In the silastic band group, five patients had suffered from lower abdominal pain. One patient had had pain for two months and this then resolved. Two patients had been reviewed before six months because of the pain, but no abnormality was found on examination. A further patient had had a diagnostic laparoscopy because of the pain and again no pelvic abnormality was detected. In each patient the pain was situated mainly on the left side.

Menstrual problems

There were no significant differences between diathermy and the silastic band technique in the

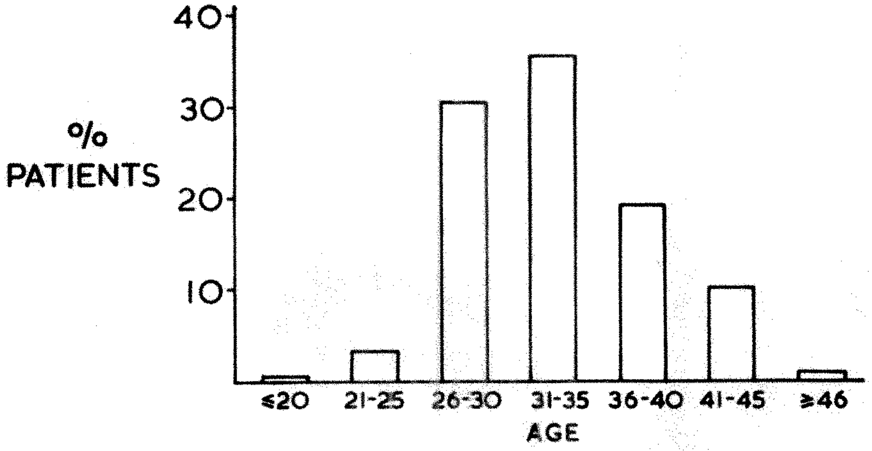

FIG. 1

Age distribution of women who were sterilised.

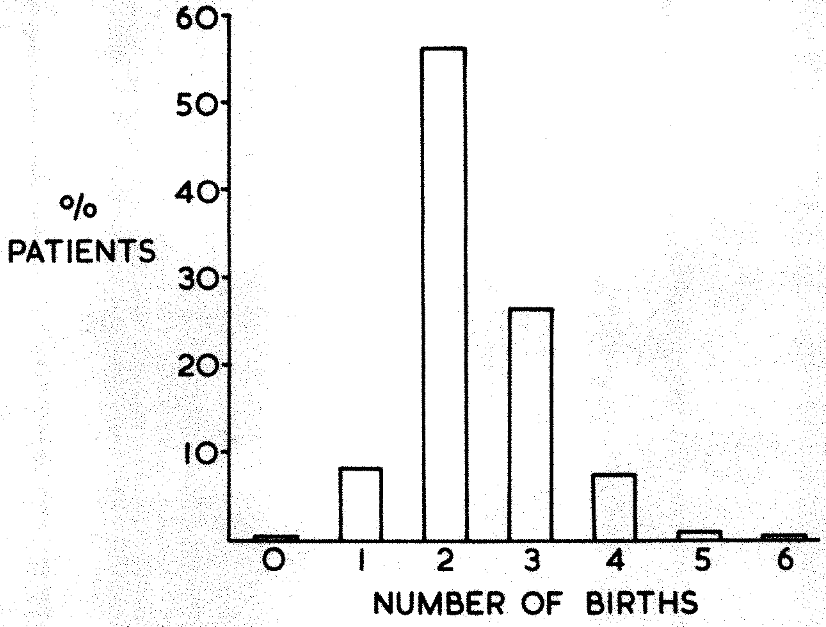

FIG. 2

Previous number of births (at more than 28 weeks gestation) in 530 women who were sterilised.

TABLE I

Patients' assessments of change in menstrual blood loss since sterilisation

Method of contraception	Periods heavier	Periods lighter	No change
	Percentage of patients reporting		
Oral (n = 289)	49	8	43
IUCD (n = 55)	22	22	56
Barrier (n = 106)	28	5	67
None (n = 77)	38	6	56
Total (n = 527)	40	9	51

TABLE II

Patients' assessments of change in menstrual pain following sterilisation

Method of contraception	Increased menstrual pain	Less menstrual pain	No change in menstrual pain
	Percentage of patients reporting		
Oral (n = 289)	31	3	66
IUCD (n = 55)	13	7	80
Barrier (n = 106)	18	2	80
None (n = 77)	29	1	70
Total (n = 527)	26	3	71

nature or incidence of menstrual problems. In presenting the results below, data from both groups had been pooled and are detailed in Tables I to III. Forty-nine per cent of patients previously on the pill and 38 per cent of those who used no contraception reported that their periods were heavier. Furthermore, 31 per cent of patients previously using the pill and 29 per cent of patients previously using no contraception reported an increase in menstrual pain. However, only 9 per cent of all patients said that they now had more bother with their

TABLE III

Patients' assessments of change in menstrual pattern

Method of contraception	Percentage of patients reporting: More trouble	Less trouble	No change in menstrual trouble
Oral (n = 289)	10	13	76
IUCD (n = 55)	2	38	60
Barrier (n = 106)	8	9	83
None (n = 77)	11	12	77
Total (n = 527)	9	15	76

periods, and 15 per cent of all patients reported less bother.

Sexual problems

No changes in sexual attitudes were reported by 253 (48 per cent) patients whereas 221 (42 per cent) said that they felt more relaxed. Fifteen patients (2·8 per cent) said their sex lives had improved and 35 (6·6 per cent) reported a deterioration, usually associated with lack of libido. Three patients (0·6 per cent) now had no partner.

Regrets

Twenty-seven patients had some regrets about sterilisation, but only four of them had thought about reversal. The reasons for regret included deterioration in sex life (three patients) and menstrual problems (one patient). Two patients had been sterilised with a medical indication (one diabetic and one who had a cerebral thrombosis on the pill). One patient regretted the permanency which had been brought home to her when her son nearly drowned. Another patient was bored at home and wanted another baby, while one who was sterilised for financial reasons had had second thoughts. Only two patients regretted the procedure because they had changed their partner. A further patient had become alarmed by adverse newspaper reports.

DISCUSSION

This study is an attempt to assess problems associated with two methods of laparoscopic sterilisation currently used widely in Britain. By questionnaires and direct interview we achieved a 94 per cent follow-up rate. Our main objectives were to identify problems associated with the two methods of sterilisation that would warrant further study.

The silastic band method had a high incidence of immediate postoperative pain (Templeton *et al*, 1977; Lee and Baggish, 1976; Pelland, 1977). In all but a very few patients this lasted only 12 hours and few patients had a disturbing recollection of the pain at two weeks. Besides this problem, there were no differences in patient acceptance of the two methods at six months.

There were no significant differences between diathermy and the silastic band method in the incidence of menstrual problems. At six months, 40 per cent of all patients reported that their periods were heavier and 26 per cent reported that they were more painful. Of 183 patients previously using barrier methods or no contraception, 32 per cent reported increased menstrual blood loss and 22 per cent reported more pain. However, the subjective nature of this assessment is emphasised by the finding that, except in the IUCD group, only around 9 per cent admitted that their periods were more bother since sterilisation. There was an unexpected discrepancy between the patients who previously used barrier methods and those who used no contraception in that there was a higher proportion of non-users who reported heavier and more painful periods. A study involving the objective measurement of menstrual blood loss following sterilisation by tubal diathermy, silastic bands and spring-loaded clips is thus indicated; to date there has been only one such study (Kasonde and Bonnar, 1976), and no increase in blood loss was detected in 23 women followed up for 12 months following tubal ligation.

Schwyhart and Kutner (1974) in their review of the literature reported lower libido or worse adjustment in 2 to 25 per cent of women following sterilisation. We found that 6 per cent of patients complained of a deterioration in their sexual relations. There is a suggestion that couples who seek vasectomy adjust better (Wortman, 1975). Possibly this is associated with the type of patient who seeks vasectomy (Howard, 1978), or vasectomy couples may receive better counselling than those seeking tubal occlusion (Bancroft, personal communication). At six months, 5·1 per cent of our patients had some regrets but only four patients considered reversal. Most British reports suggest that 3 to 4 per cent of patients have some regret about sterilisation (Thomson and Templeton, 1978). As the mean age of the women with regrets in our study was 33·7 years, we do not agree that sterilisation should be restricted to women over 30 years (Sim *et al*, 1973, Winston, 1977).

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HAEMOPERITONEUM DUE TO CORNUAL ENDOMETRIOSIS AFTER LAPAROSCOPIC STERILISATION

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Summary

We present a patient with a haemoperitoneum due to bleeding from an area of endometriosis of the uterine cornu six years after laparoscopic sterilisation.

CASE REPORT

MRS L.B. was a 28-year-old para 4 who had previously had a laparoscopic sterilisation by diathermy and division of the isthmic portion of the uterine tubes in 1971. In 1973 she had had a curettage for irregular menstrual periods. She gave a history of lower abdominal pain and severe dyspareunia for the previous six months, and occasional dysmenorrhoea for a similar period. Her last menstrual period occurred on 27th October 1977, and she was admitted as an emergency on 9th November 1977.

On examination she was anxious but not pale, jaundiced or cyanosed. The pulse rate was 88 beats per minute, the blood pressure 105/65 mm Hg, and the temperature 36·8°C. General examination showed no abnormality, but there was marked abdominal tenderness, maximal in the hypogastrium and the right iliac fossa. On pelvic examination there was cervical excitation pain, and a mass could be felt on the right side of the posterior vaginal fornix. The patient's blood was 0 rhesus negative, the haemoglobin was 11·4 g/dl, the white cell count 13 000/mm^3, the packed cell volume 34·2, and the erythrocyte sedimentation rate 7 mm in the first hour. A pregnancy test was negative and microscopy of the urine showed no abnormality. A diagnosis of possible ectopic pregnancy was made and an intravenous infusion was commenced.

The patient had a laparoscopy which confirmed the presence of a pelvic haematocoele, but the reason for this was not apparent. A laparotomy was therefore done and 1500 ml of blood evacuated from the pelvis and abdominal cavity. It was found that both Fallopian tubes had been previously divided by diathermy and there was no evidence of ectopic pregnancy. The ovaries appeared normal, the right one containing a corpus luteum. There was bleeding from a small lesion in the right uterine cornu. This lesion was excised and the uterine cornu repaired with Dexon. No other abnormality was found. The patient was transfused with 1500 ml of whole blood during and after surgery. She made an excellent postoperative recovery, and was discharged home on the tenth postoperative day.

Histological examination of the excised lesion of the right cornu showed myometrial tissue containing irregularly scattered foci of endometrial tissue (Fig. 1). The attached serosa also contains foci of endometriosis. Small areas of haemorrhage and moderate round cell inflammatory infiltration were present.

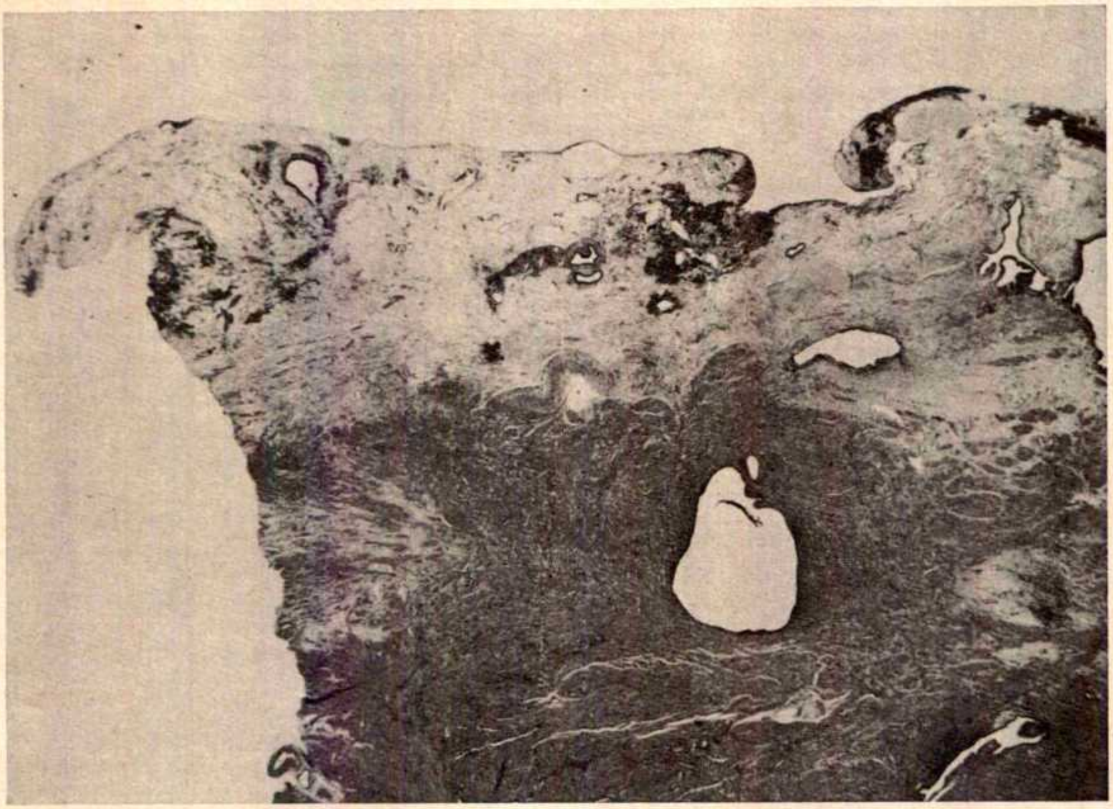

FIG. 1

The photograph illustrates endometriosis of the uterine cornu (haematoxylin eosin ×16).

We conclude that our patient had a haemoperitoneum due to bleeding from cornual endometriosis six years after laparoscopic sterilisation. No similar case report appears to exist.

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We thank Mr D. H. G. Cowie for help with the clinical management of our patient and for permission to publish this report.

Note: Dr F. I. Uri is now Consultant Obstetrician and Gynaecologist, P.O. Box 921770, Amman, Jordan.

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REAL-TIME ULTRASOUND B-SCAN AS AN AID TO ANTEPARTUM FETAL HEART RATE MONITORING IN MULTIPLE PREGNANCY

CASE REPORT

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Summary

Real-time B-scan was found useful in locating the fetal hearts before antepartum fetal heart rate monitoring by Doppler ultrasound in a patient with a triplet pregnancy.

MONITORING fetal wellbeing in a triplet pregnancy poses many problems. Placental function tests such as assay of urinary oestrogen and human placental lactogen may be helpful in the management of singleton and twin pregnancies but normal levels for triplet pregnancies are not known. Fetal growth may be assessed by means of ultrasound cephalometry but centile curves for triplet pregnancies are not available. Non-stressed antepartum fetal heart rate (FHR) monitoring is a good guide to fetal wellbeing (Rochard *et al*, 1976), but monitoring in multiple pregnancies, certainly with triplets or more is laborious, and doubt frequently exists as to whether all fetal hearts have been monitored.

We recently had a patient in whom three fetuses died *in utero* at 36 weeks gestation. Though FHR monitoring had not been employed, one fetal heart was definitely heard on the day before delivery and biochemical tests of fetal wellbeing had been normal. We decided, therefore, to attempt to monitor each fetus in another triplet pregnancy by means of Doppler ultrasound, having previously located each fetal heart by real-time B-scan.

CASE HISTORY

Clinical features

Mrs N.C. was a 24-year-old primigravida whose last menstrual period was on 16th May, 1978. Triplets were diagnosed by ultrasound B-scan at 21 weeks gestation. Eight weeks later the patient was admitted to hospital for rest. The maternal condition remained stable during her stay in hospital and fetal wellbeing was assessed by means of serial ultrasonic head and trunk measurements, plasma and urinary oestrogens, human placental lactogen, and electronic FHR monitoring. Adequate growth was noted on B-scan and placental tests showed a steady rise. It was hoped to allow pregnancy to continue to 36 weeks gestation and then to deliver the babies by elective Caesarean section.

At 35 weeks, the patient went into labour and the membranes ruptured spontaneously. A Caesarean section was done at which three live healthy male infants were delivered. They weighed 2·26 kg, 2·44 kg and 2·31 kg and their respective one-minute Apgar scores were 8, 5 and 7; all three babies had an Apgar score of 9 at five minutes. Mother and babies did well and were discharged home on the ninth postoperative day.

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Monitoring of FHR

A portable real-time B-scan Unit, the Unirad Sonofluoroscope I, with a 3·5 Mega Hertz transducer was used to locate each fetal heart. Continuous FHR recordings were obtained using a Hewlett-Packard 8030 A Cardiotocograph, with a paper speed of 2 cm/minute.

Monitoring was done at the bedside with the patient slightly tilted to the left side. The lie and presentation of each fetus was assessed with the real-time unit and each fetus was referred to as A, B or C according to the order of presentation. The fetal heart of triplet A was visualized on the screen and the transducer angled in such a way as to give the clearest picture of heart movements. This angle would then be used to direct the Doppler ultrasound beam at the fetal heart. The exact position of the fetal heart in relation to the transducer was then determined by running a finger between the transducer and the skin noting when the fetal heart became obliterated on the screen. Having located the fetal heart, and knowing the angle to direct the Doppler ultrasound beam, the Doppler transducer was then held in position by the nurse carrying out FHR monitoring. After a continuous FHR recording of at least 15 minutes, the fetal hearts of triplets B and C were located and monitored in turn in a similar fashion. By checking the fetal heart positions of the other two fetuses during each period of monitoring we ensured that we were in each case monitoring a different fetus. A tocotransducer was not used to record uterine contractions as this would have been cumbersome due to the extreme abdominal girth. Fetal movements were recorded on the FHR tracing by the monitoring nurse.

RESULTS

The fetuses remained in the same position relative to one another over the six week period during which monitoring was done, though fetus B changed from a cephalic to a breech presentation the day before delivery. FHR monitoring was done twice weekly and the final record was obtained on the day of delivery. All three fetuses were active at the time of investigation and responded to movement with accelerations in heart rate. All tracings obtained were of good quality and indicative of fetal wellbeing.

DISCUSSION

Non-stressed antepartum FHR monitoring is considered by us to be an integral part of the management of 'high risk' pregnancies. Multiple gestation, especially triplet pregnancy, is associated with a high perinatal wastage (Daw 1978). FHR monitoring, until now, has been difficult to perform and evaluate for triplets but we have overcome some problems by combining real-time and Doppler ultrasound to obtain a satisfactory recording of FHR for each fetus. We believe this represents an advance in the management of multiple pregnancies.

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British Journal of Obstetrics and Gynaecology
August 1979. Vol. 86. pp 668–669

BOOK REVIEWS

Epidural Analgesia. By P. R. BROMAGE. Pp v+746 with 286 figs and 66 tables. W. B. Saunders Company, London, 1978. Price: £21.75.

WHAT can one say in a brief review of a 750-page book devoted to one technique of pain-relief, other than express esteem and approval? Having read every one of those pages, it is my opinion that not one is irrelevant or a waste. Professor Bromage has drawn upon a vast personal experience of the technique of extradural block and widely-spread reading of the literature relating to the procedure, in producing what must be the definitive work on the topic. The first half of the book is devoted mainly to the relevant features of anatomy, physiology and pharmacology. These are so intensively discussed—at times the author seems to be conducting a love affair with the central nervous system—that it illuminates many of the rather obscure growing points of the sciences of neurophysiology and neuropharmacology. There follow chapters on the practical applications of epidural analgesia in the clinical fields of obstetrics, surgery, pain clinics and diagnostic procedures. I can write with confidence only in regard to the first of these. The 90 pages devoted to obstetric matters contain much sound advice, based mainly upon the extensive clinical experience of Bromage and his colleagues in Montreal's Royal Victoria Hospital. As is to be expected, in some particulars the advocacy does not match that of ourselves or of others in the United Kingdom, but the differences are very rarely unreconciliable. The penultimate chapter—Complications and Contraindications—is a sober and well-balanced account, and would do much to calm the fears of those who remain under the spell of apocryphal horror tales about the disasters which may befall the patient to whom an epidural is given. In this context, my only reservation was with regard to the author's support—admittedly tentative—for the policy of initiating an epidural in a patient on a 'mini-heparin' regimen. There are understandably many points with which one could quibble or find fault in this book—I remain uneasy about Bromage's explanation of the escape of pain through an established block; I see little merit in the inclusion of adrenaline in the solution of bupivacaine used for pain relief in labour, or in waiting until the end of the first stage before attempting to block the sacral roots—but these detract to no significant extent from the tremendous value of the work. The volume itself is excellently produced, and the many figures are distinct and informative. Furthermore, what a joy it is to read a medical work written by a master of English prose unfettered by the current and lamentable constraints imposed by the Editors of all our leading Journals. The price is not high in contemporary terms, and the contents would amply reward investment by obstetricians, anaesthetists, and departments of both disciplines.

J. Selwyn Crawford

Reversibility of Female Sterilization. Edited by I. BROSENS and R. WINSTON. Pp vi+194 with figures and tables. Academic Press, London, 1978. Price: £7.50/$15.50.

THIS volume contains both the papers and the discussion at a symposium in June 1977. It includes chapters on ovum transport, ultrastructure and experimental microsurgery as well as tubal pathology. Surgical techniques are then described and discussed and the results recorded for various procedures. Both in the papers and the recorded discussions every aspect of tubal surgery is mentioned and there is an enormous wealth of experience which the reader can draw upon. The results presented suggest that careful, meticulous time-consuming surgery with or without the use of a microscope helps a significant number of patients to achieve a pregnancy following reversal of a previous sterilisation. Opinions are variable regarding the criteria necessary before attempting operation which makes comparison impossible, but the message is clear that there is considerable hope for most patients. The participants conclude that comparison of results under the infinitely variable conditions found at operation is not immediately possible (but may become so with really accurate recording), and neither can the findings at operation be correlated with the future prognosis as regards pregnancy. The book should be essential reading for any surgeon with an interest in infertility and despite its 'typewriter' type its hard back makes it a pleasure to handle and read.

D. W. T. Roberts

Endometrial Cancer. Edited by M. G. BRUSH, A. KING and R. W. TAYLOR. Pp v+459 with 197 figs and 123 tables. Bailliere Tindall, London, 1978. Price: £16.50.

WHAT does the clinician want to know about endometrial cancer and its treatment? He wants to know what sort of women get it, does oestrogen treatment predispose, is the cyclical use of a progestogen advisable, the place of radiotherapy and which patients respond to progestogens. Final answers to these questions are not available, but the authors of Endometrial Cancer provide authoritative opinions on all these topics which were up-to-date when they prepared the papers for the Second International Symposium on Endometrial Cancer and Related Topics at St Thomas's Hospital in March 1977. The editors have produced a valuable survey that will help working clinicians and provide a useful collection of opinions for academics. The contributors diverge most when discussing oestrogen treatment and endometrial cancer. The published studies are critically reviewed by Mack and suggest a definite association. He accepts that oestrogen treatment may be only the trigger that activates the tumour in a predisposed woman but points out that from the practical point of view 'causal' means that the knowledge of an association can be used to minimise the future occurrence of the condition. The workers from King's College Hospital show that unopposed oestrogen treatment increases the occurrence of endometrial hyperplasia and that this effect is minimised by the cyclical use of a progestogen. Other papers tend to confirm the view that adenomatous hyperplasia may precede invasive cancer. Both Campbell and Hutton and their co-workers shows that oestrogen treatment, although relieving flushes and vaginal dryness, causes unphysiological elevation of plasma oestrone levels. This is hormone treatment rather than hormone replacement. Aylward and his team, supported by Audrey Ward, show that while ethinyl oestradiol causes abnormalities of coagulation this is not the case with Harmogen or Progynova; Premarin caused some small changes. There are useful reviews of the relative merits of surgery and radio-therapy from Vera Dalley, Lees and Joslin. Progestogen therapy is reviewed by Kohorn who shows that one-third of patients respond to high dose regimens and provides information on dosage, blood levels and response. The sections on the intracellular binding of oestrogen and progesterone are of great interest and may in time have clinical application in providing a prognosis for progestogen treatment. Most published proceedings of meetings have value only for the curriculum vitae of the contributors. This book is an exception and provides in one volume information that is scattered in many journals and which has not reached the standard texts.

D. B. Paintin

Clinical Hypertension—Second Edition. By N. M. KAPLAN. Pp vii+405 with figures and tables. The Williams & Wilkins Co, USA, 1978. Price: £26.65, $41.00.

THIS well written volume is intended for the practising physician. The approach to the problem is orthodox, and sometimes contentious: hypertension, says the author, "is mankind's most common disease". Many would dispute this simplistic statement, particularly obstetricians who have a unique view of the lives of young hypertensive women who by no criteria can be said to be diseased. Most of the work is subdivided into chapters dealing with the different clinical presentations of hypertension. In addition, Chapter 3 covers treatment and the 16 pages of Chapter 5 summarize what is known about the renin-angiotensin system. The chapter on treatment is inevitably less interesting to the English reader because so many of our routine treatments are not available in the USA; in early 1978 propranolol was the only β-adrenergic blocking agent approved for general use there. There is a good chapter covering hypertension with pregnancy and with oral contraceptive agents. Although there is little that is new for the obstetrician, it is up-to-date, concise, with a good balance between the obstetric and medical viewpoints of the problems. The last paragraph briefly mentions that more than half of American women over the age of 50 take oestrogens for menopausal or postmenopausal indications. The vascular consequences of this therapeutic epidemic will no doubt make interesting reading if Dr Kaplan can give us a third edition in a few years time. The style throughout is light and enjoyable, but the content is detailed and authoritative. The book is recommended to clinicians who wish to keep track of the subject without needing to be up with the very latest developments.

C. Redman

British Journal of Obstetrics and Gynaecology
August 1979. Vol. **86.** pp 670–672

CORRESPONDENCE

Maternal Serum Alpha-fetoprotein and Diabetes Mellitus. Wald, N. J., Cuckle, H., Boreham, J., Stirrat, G. M., and Turnbull, A. C. (1979): *British Journal of Obstetrics and Gynaecology*, **86,** 101.

From: J. F. Pedersen and L. Mølsted-Pedersen.

Sir,

Dr Wald and his colleagues have kindly sent us a proof of their paper in which they showed that serum alpha-fetoprotein (AFP) levels were significantly lower than normal in diabetic pregnancies. They could, however, not explain this result. The publication of our report on early growth retardation in the diabetic pregnancy (Pedersen and Mølsted-Pedersen, 1979) made them think that this phenomenon might explain their finding.

We think they are right, and have rearranged the data in their Tables I and II to support this viewpoint. We have plotted maternal serum AFP against gestational age for their controls and drawn lines to delineate the total range of the controls (Fig. 1). The AFP values from the 27 diabetic pregnancies are plotted on the same figure. To avoid bias, only the first value from each pregnancy together with the two corresponding controls have been used.

Six AFP values fall below the range of the controls (patients No. 1, 3, 4b, 9, 12 and 19). These six values as a group behave as if the pregnancies were 2½ to 3 weeks younger. This subgroup differs from the remainder by a lower average birth weight, 2985 g as against 3310 g, in spite of a similar gestational age, 38 weeks as against 37 4/7 weeks.

In 35 insulin-dependent pregnant diabetic patients with reliable menstrual data, we found the fetal size (crown-rump length as estimated by ultrasound in weeks 7 through 14) to be on an average 5·4 days too small. Ten of them had a fetal size below normal range. As a group these fetuses were 15 days too small in early pregnancy. They also had a significantly lower birth weight, 2800 g as against 3580 g, although the gestational age was similar (Pedersen and Mølsted-Pedersen, 1979).

We believe that the unexpected results of Dr Wald and his colleagues are fully explained by, and further support, our observation of an early growth retardation in the diabetic pregnancy.

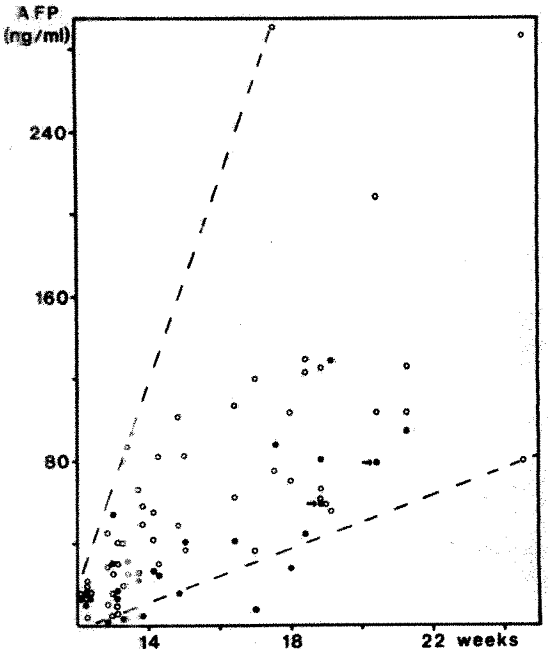

FIG. 1

Scattergram showing distribution of serum alpha-fetoprotein (AFP) against gestational age in 27 pregnant diabetic patients (closed circles) and in 54 matched controls (open circles). Range of controls indicated by dotted line. Six diabetics show AFP levels below range of normals. Two diabetics had a malformed fetus (arrows).

Although the figures are very small, it is of theoretical interest, and in line with our own findings, that the two cases of fetal malformation showed AFP values low in the normal range (patients No. 5b and 13a; Fig. 1). If this suggests an early growth retardation, it must have taken place in the vulnerable period of organogenesis.

Yours, etc,

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REFERENCE

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Cervical Cancer and Cytology Screening in New Zealand. Green, G. H. (1978): *British Journal of Obstetrics and Gynaecology*, **85**, 881.

From: G. Johannesson and N. E. Day.

Sir,

In the recent article by Green, the trends in the incidence and mortality rates for cervical cancer in New Zealand have been examined in relation to the level of cytological screening. These data show that screening as practiced in New Zealand has had no appreciable effect on either morbidity or mortality. The author then claims that these data throw doubt in general on the value of cervical screening and that "the significance of the 'pre-cancers' revealed by cytology and the value of population screening would seem to be doubtful". We feel that, given the data presented, this conclusion is unjustified.

Screening will have little effect on future mortality or morbidity if either:

(1) Tumors grow too quickly to be more than rarely detected in a preclinical or precancerous state by screening, unless screening is repeated with an impractical frequency; or

(2) Treatment of those detected in the preclinical disease state does not appreciably improve prognosis; or

(3) Screening is confined to those at low risk for the disease.

To show that the first point pertains, one would have to show that invasive tumors occur among those with previous negative smears with a frequency near that of the general disease incidence. Data from British Columbia (Fidler *et al*, 1968), Aberdeen (MacGregor, 1976), Finland (Hakama and Rasanen-Virtanen, 1976) and Iceland (Johannesson *et al*, 1978), for example, demonstrate convincingly that invasive tumors seldom arise in those with a negative smear. The deficit in incidence among those with a prior negative smear is too great to be the result of confounding factors (Bross, 1967).

The second point depends on the thoroughness of the follow-up of those detected with precancerous lesions. If these cases are poorly controlled then progression to an advanced tumor is a considerable possibility and the effectiveness of the screening is diminished. However, experience from, for example, the centres mentioned above demonstrates that there should be almost zero mortality resulting from a treated preclinical lesion.

Failure of a cervical cancer screening program to reduce mortality, given that both the screening itself and the treatment of detected lesions are properly conducted, must then result from a failure to screen those at higher risk. Before accepting, however, that this failure is inevitable, evidence is required of an effort to identify and screen high risk women in the program population. In New Zealand, in addition to the increasing risk with age seen in many countries, there is also a specific group, the Maori, with an elevated incidence of cervical neoplasia (Waterhouse *et al*, 1976). The only data Green presents on the screening rate are the number of smears read per year per thousand woman over 20 years of age, for 1962 and 1966. This measure of screening intensity is almost uninterpretable. It gives no information on the number of women in the population who have never been screened, nor the proportion of women screened by age group and race. Even if screening were completely effective, it would be impossible to predict from the above measure what effect on mortality would be expected. For example, 200 smears per 1000 women, approximately the 1966 rate in New Zealand, could well represent one woman in five returning every year. If these women, presumably the highly health conscious, were originally at one half of the risk of the rest of the population, then the largest reduction one could expect would be about 10 per cent. From Figure 3 of Green's article, a 10 per cent reduction in mortality between 1955 and 1972 due to screening would be lost among the overall trends.

Green also suggests that most of the screening was among women under 35 years of age. Less than 20 per cent of invasive tumors occur in this age group in New Zealand (Waterhouse *et al*, 1976). There is no indication that screening was even offered to older women. For the women over 35 years of age, then, Green presents no data suggesting that screening in New Zealand could have affected morbidity or mortality. For woman under 35, whose increasing mortality from the disease is stressed, increased morbidity might be expected due to changing sexual mores, with increasing sexual activity among the young. Since no data are presented on the number of women under 35 who have been screened, one is unable to evaluate the extent to which this presumptive increase might have been checked or even reversed by screening.

The results of screening programs in Finland (Hakama, 1978), Iceland and the Aberdeen region of Scotland, to name but three, demonstrate convincingly that mass screening for cervical cancer can lead to substantial reductions in both incidence of invasive disease and in mortality. The conclusion one draws from negative results as reported from New Zealand is either that the wrong subgroups of the population were selected as the main target for screening, or that the high risk groups in the population have escaped screening for reason of no general applicability.

Yours, etc,
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From: B. F. Cameron.

Sir,

I was struck by the characteristics of the sample populations for serum glucose concentration values, both random samples and 1 to 3 hour postprandial samples. The individual patients seem to be drawn from a population that is not normally distributed with respect to this variable, in that the standard deviation is a function of the variate. For the random mean glucose samples, the standard deviation is significantly correlated with the mean (r = 0·80, P <0·01, T = 0·58, P <0·01), and the correlation of mean with standard deviation is only slightly less for the 1 to 3 hour postprandial mean glucose values (r = 0·57, 0·01 <P <0·05; T = 0·36, P <0·10). Even more anomalous for a normally distributed variate, the standard deviation for the postprandial samples shows a significant *positive* correlation with the number of samples (r = 0·65, 0·01 <P <0·05; T = 0·43, P = 0·05). For a normally distributed variate the standard deviation would be expected to be *negatively* correlated with the number of samples, varying as $\sqrt{n}$. These correlations could occur spuriously if the number of measurements inversely correlated with the mean glucose. This is not the case, since there is no significant correlation of number of measurements with mean glucose either for random samples (r = 0·40) or postprandial samples (r = 0·39).

Under such conditions, a nonparametric test of correlation is the appropriate statistic for tests of association involving mean glucose. The correlations given by Widness *et al*, when appropriately calculated by use of the Kendall coefficient of rank correlation, T (Sokal and Rohlf, 1969), indicate a generally weaker association then these authors present (random mean glucose *vs* Hb AIC, r = 0·84, P <0·001, T = 0·60, P <0·01; random mean glucose *vs* birth weight, r = 0·58, P <0·05, T = 0·32, NS, P >0·10; random mean glucose *vs* birth weight ratio, r = 0·83, P <0·001, T = 0·52, P <0·05).

The fact that the conclusions of this paper are somewhat weakened is perhaps of less interest than the question as to why the mean glucose concentration variate is not normally distributed in this group of patients.

Yours, etc,
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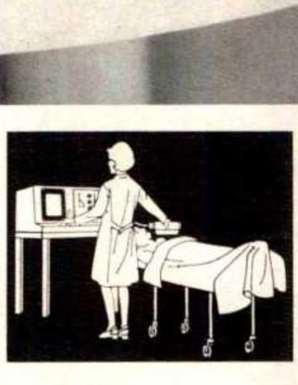

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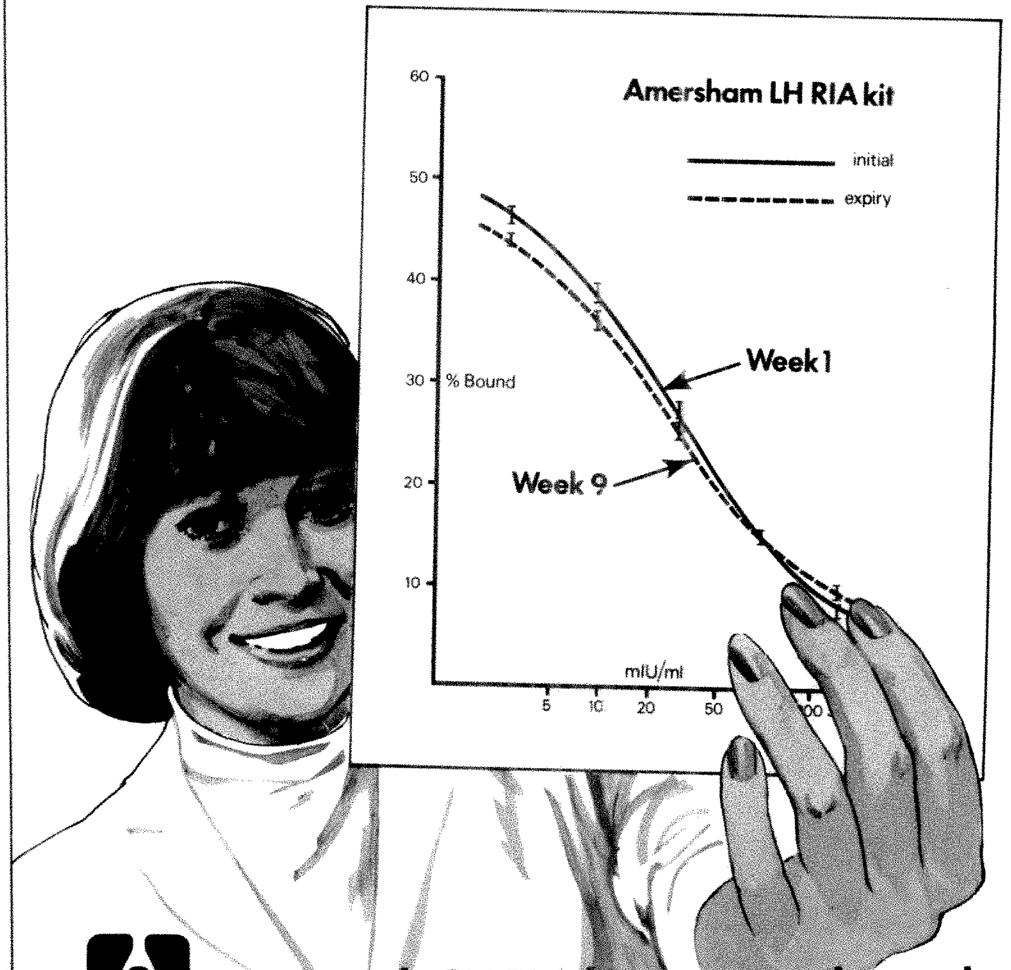

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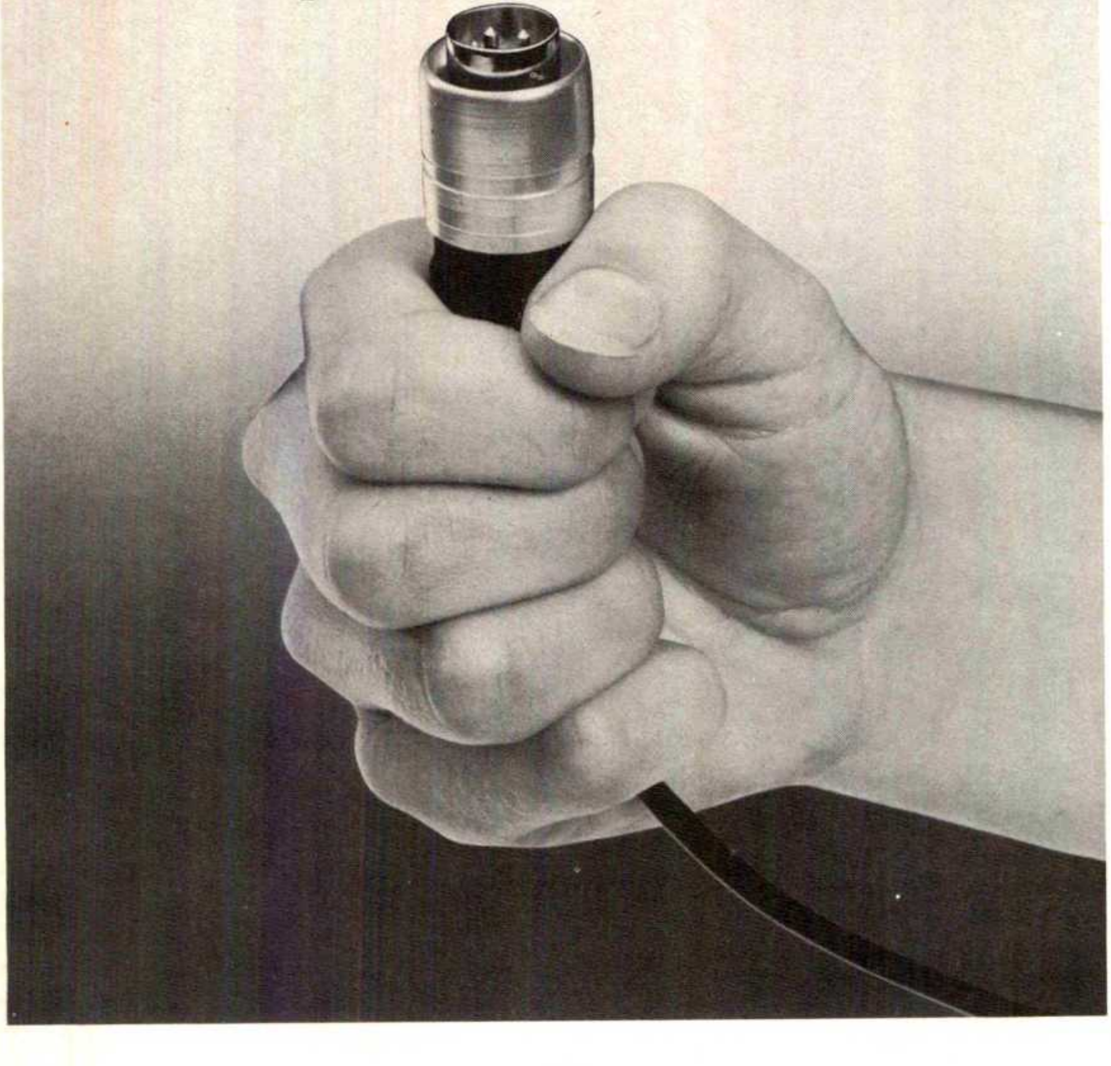

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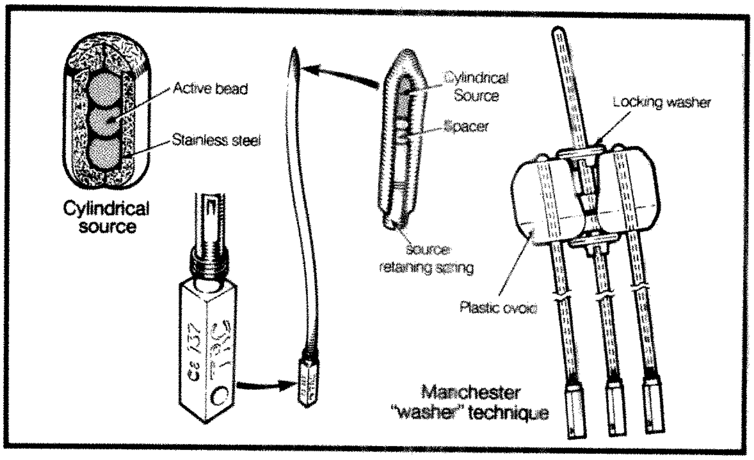

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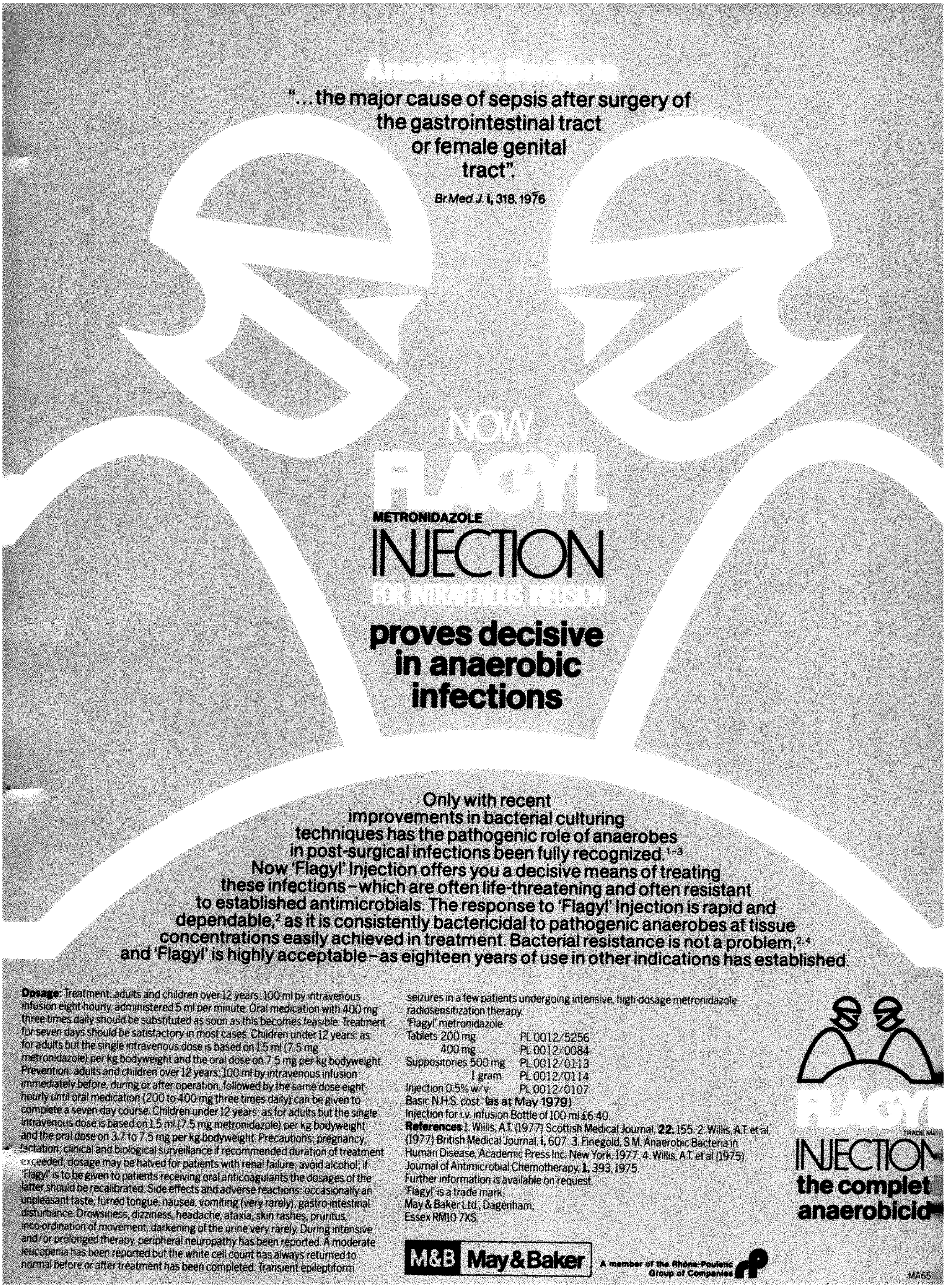

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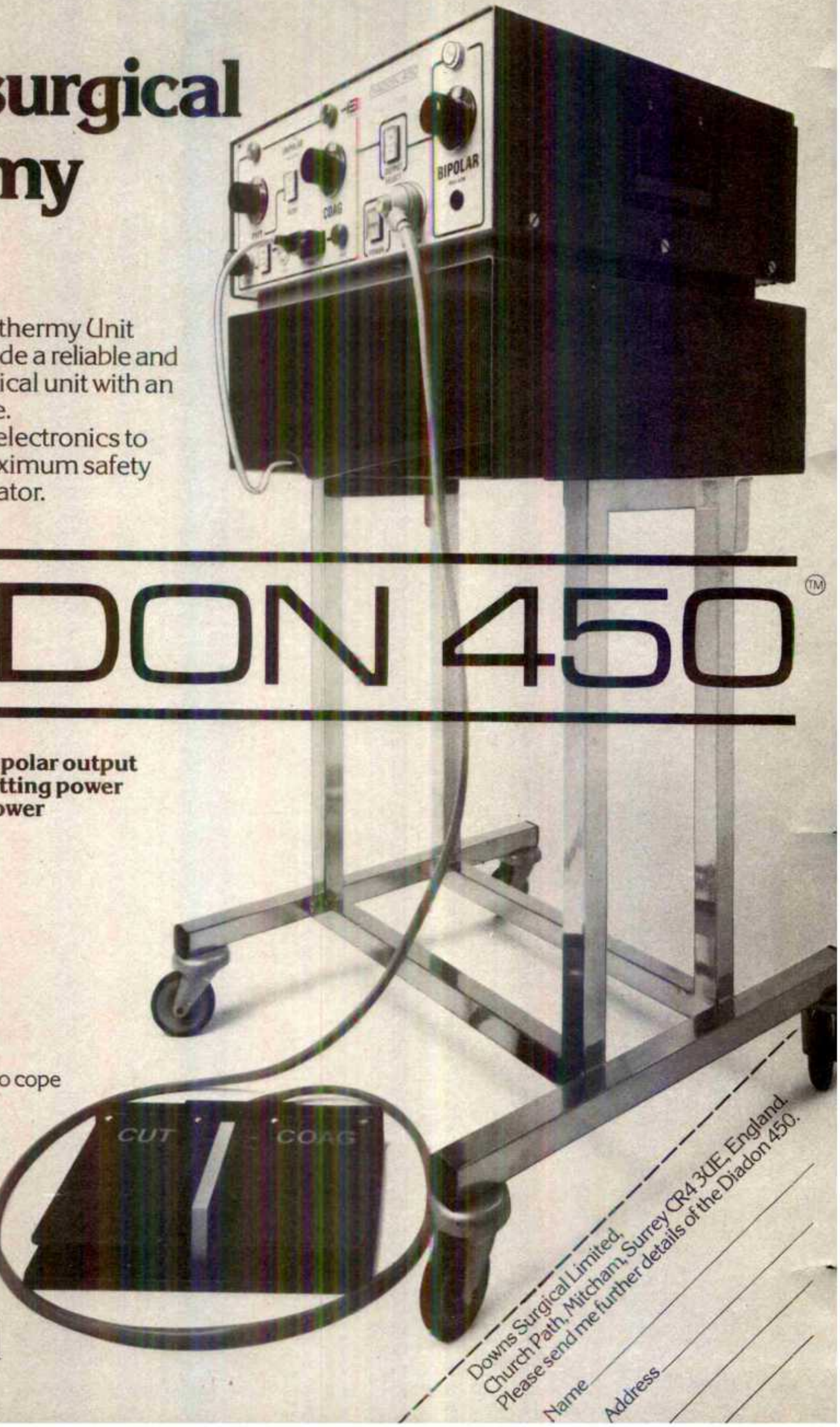

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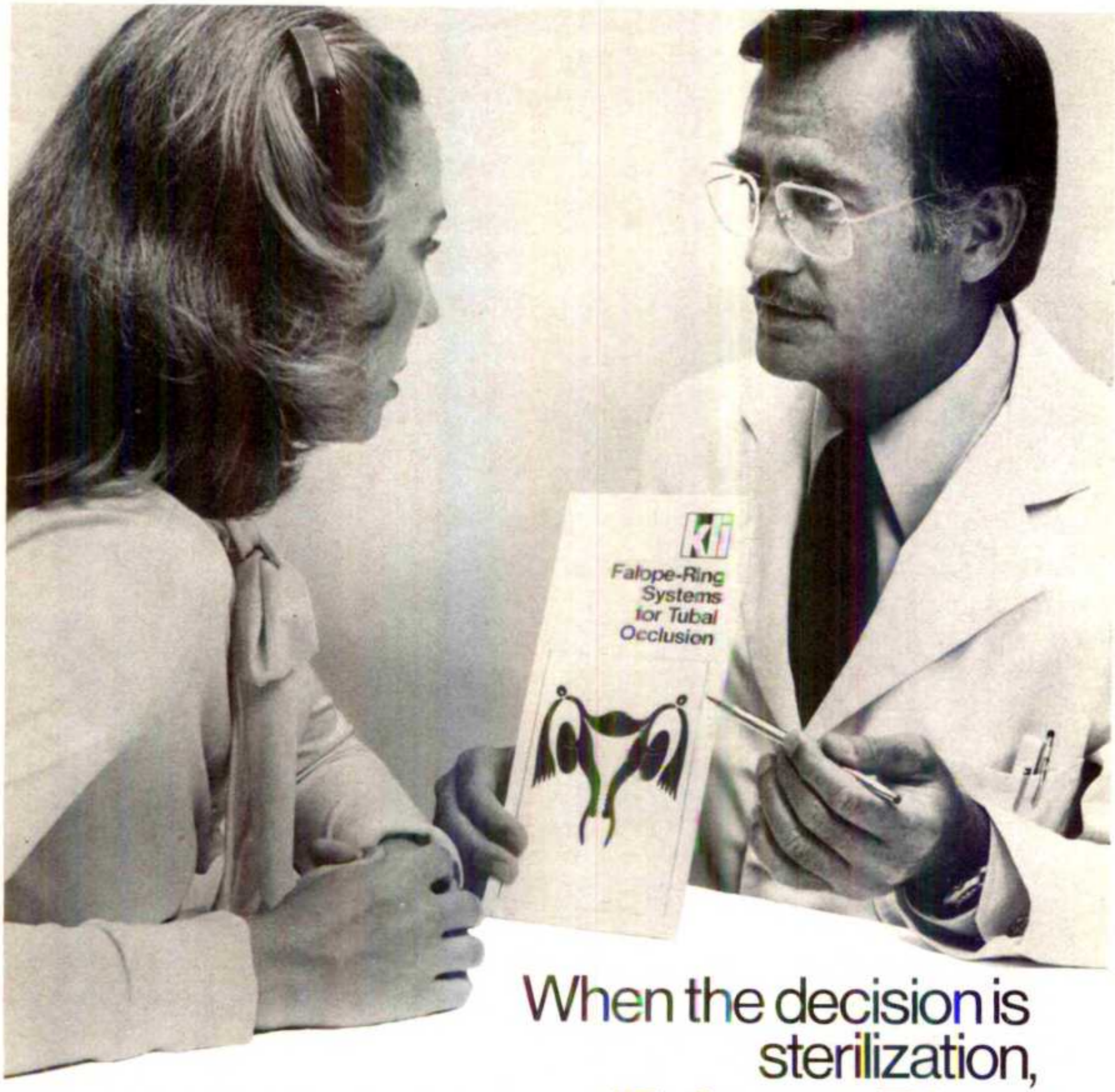

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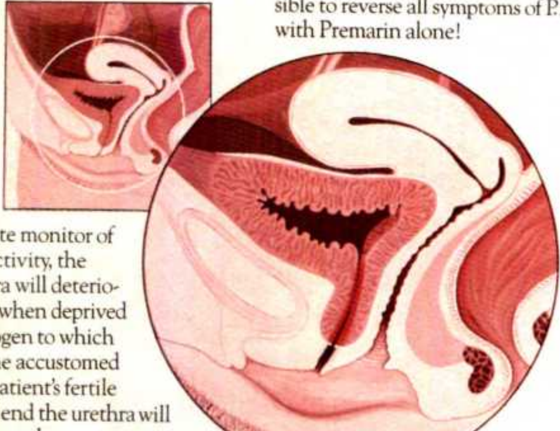
Untreated, these atrophic changes can be devastating and demoralising in their effect.[2]



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References:

1. Willington, F. L. The Practitioner. 220, 739, 1978.
2. Smith, P. J. B., Ayerst Medical Library Vol. 2, No 2, 1978.
3. Smith, P. J. B., The Practitioner, 218, 97, 1977.

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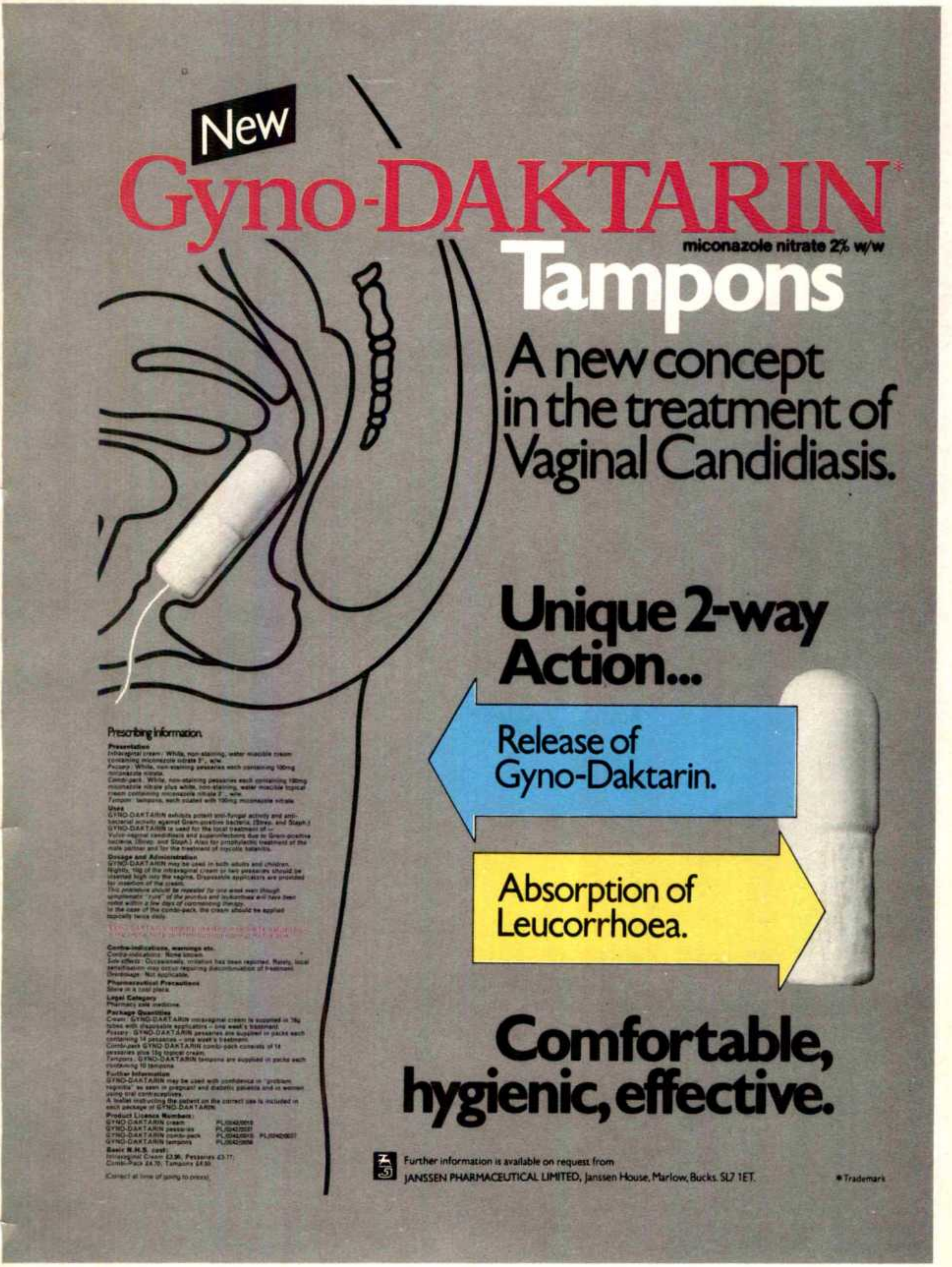

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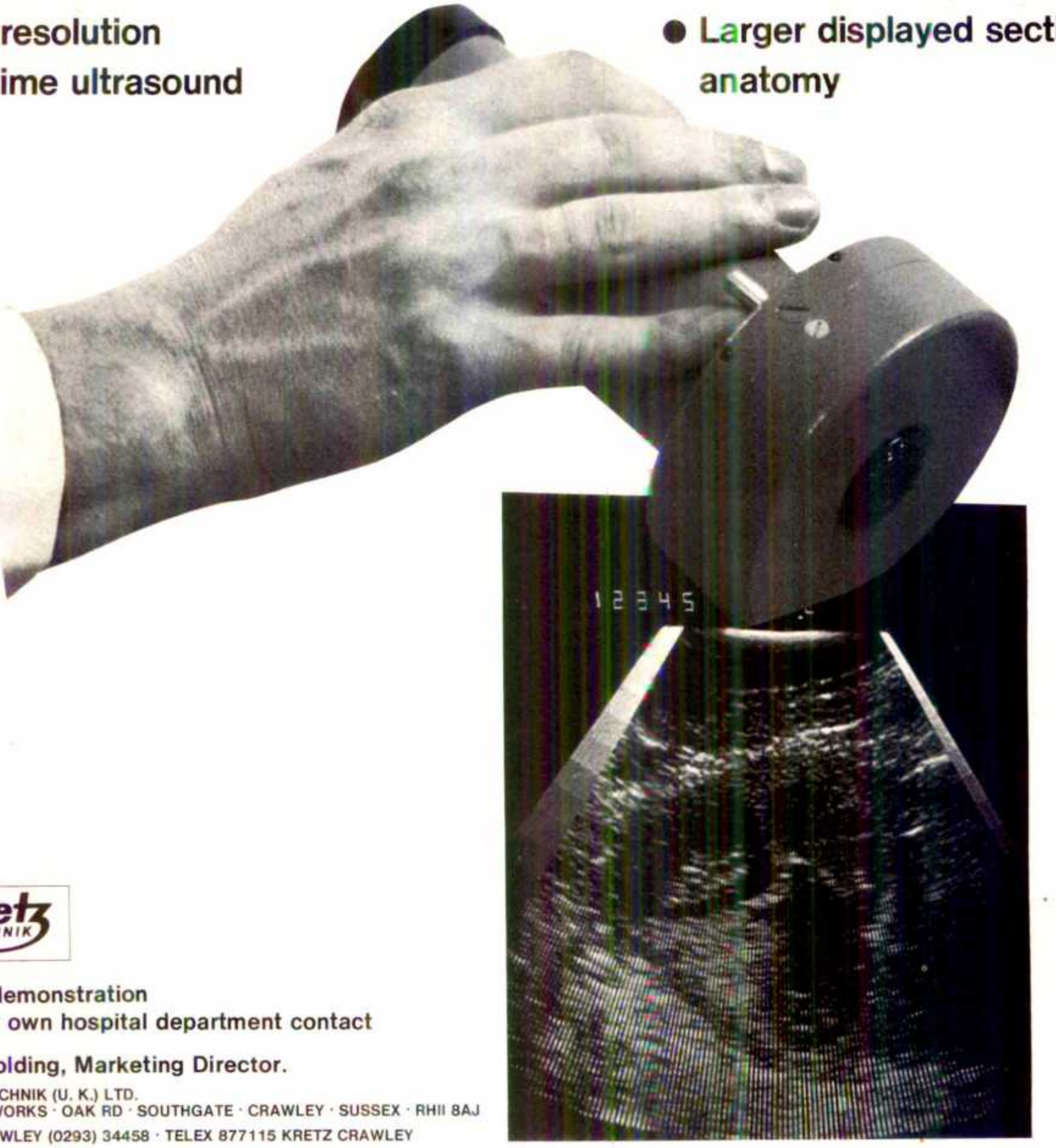

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1. J. int. med. Res. (1977) 5 (Suppl. 3): 86-91.
2. ibid., 101-108. **3.** ibid., 98-100.
4. ibid., 114-123.

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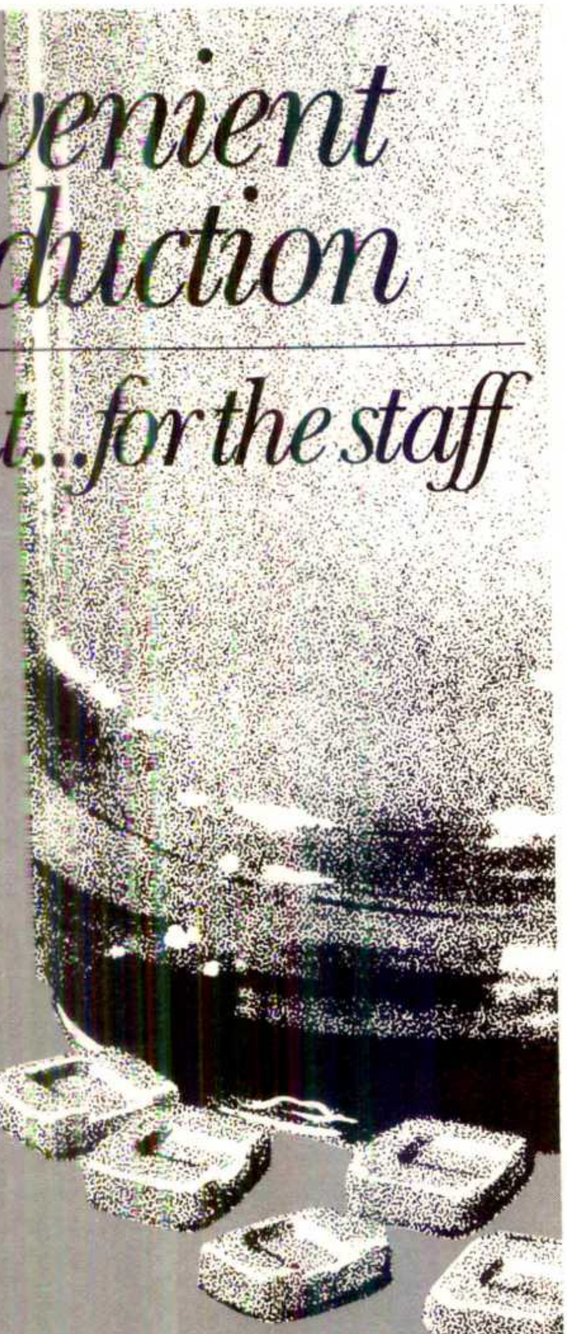

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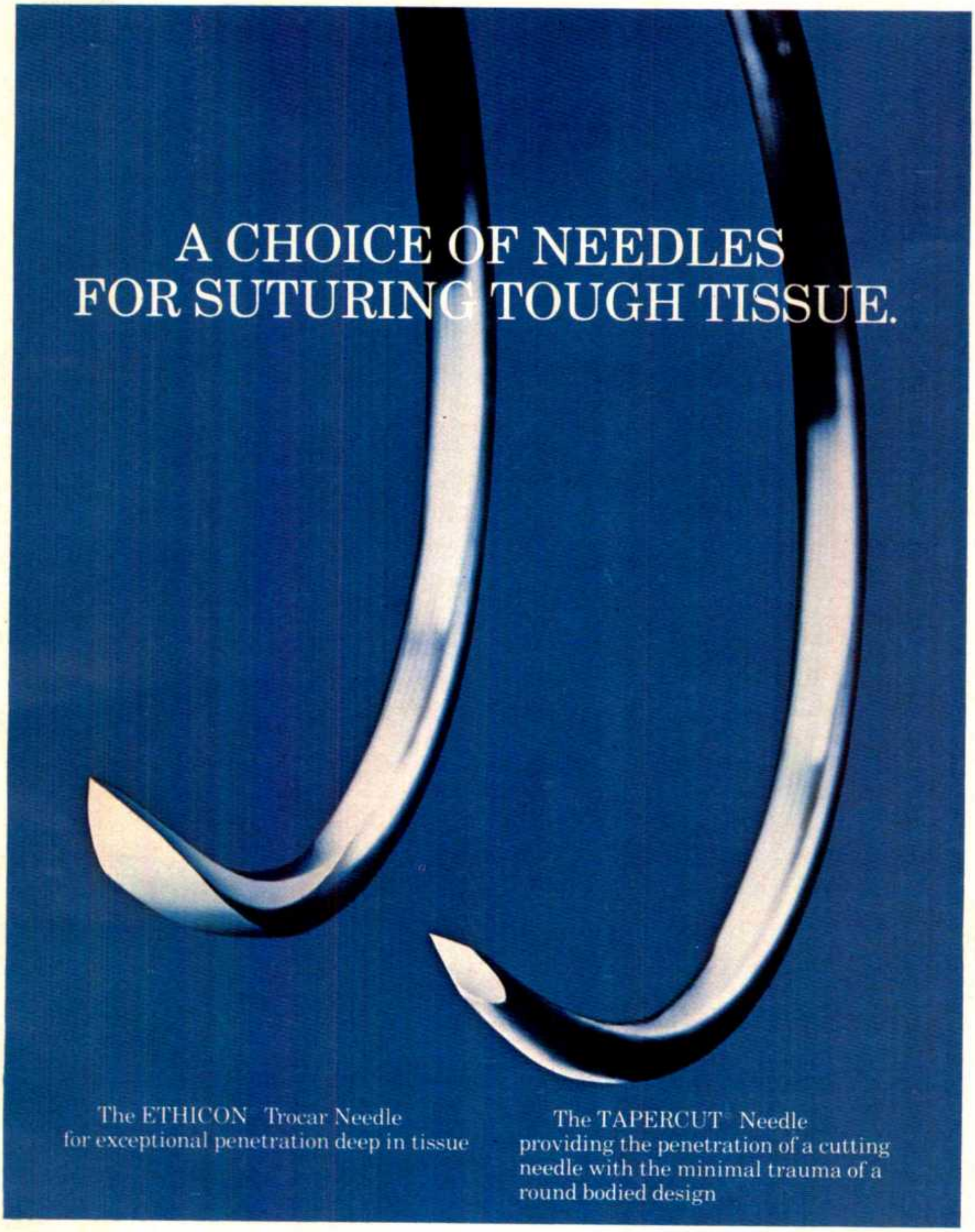
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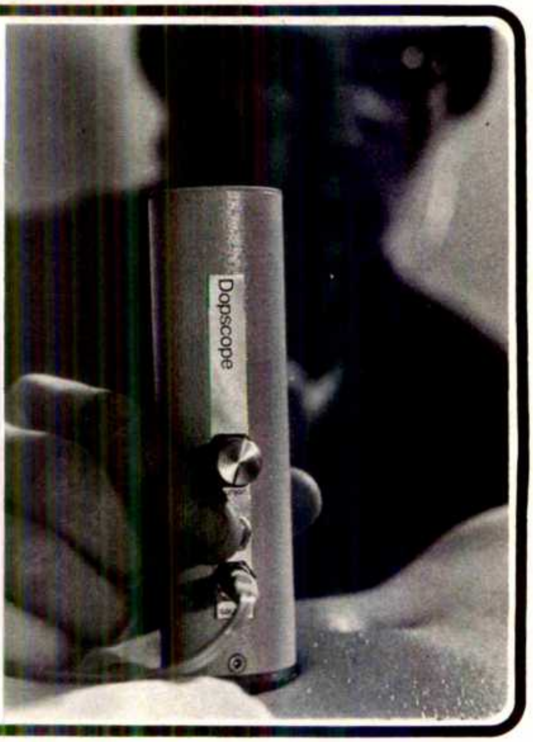

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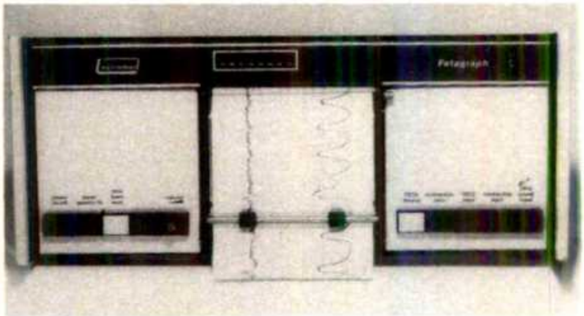

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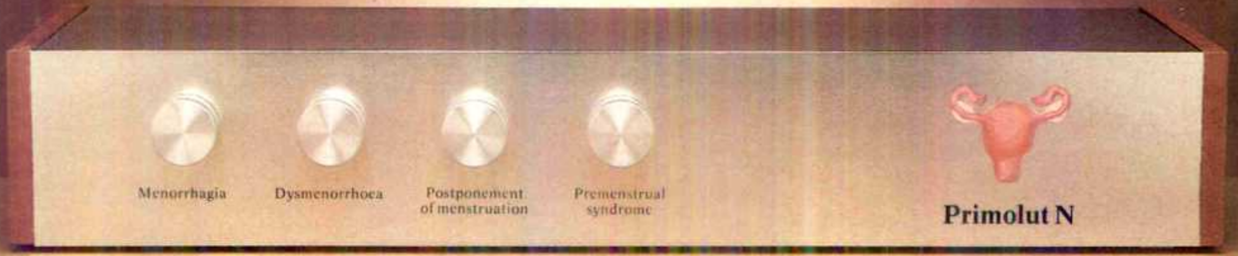

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INTRAPARTUM FETAL MONITORING PRACTICE IN THE UNITED KINGDOM

BY

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Summary

In September 1978 a postal survey was made to establish the influence of continuous fetal heart rate monitoring on clinical practice in 264 Consultant Obstetric Units in the United Kingdom. Replies were received from 244 units (92·4 per cent) and only one of these did not possess any fetal heart monitors. The approximate percentage of patients monitored during labour in these units displayed a bimodal distribution with peaks at 20 to 30 and 80 to 90 per cent, reflecting a division of opinion about the need to monitor all or only 'high risk' patients. For each hospital the ratio of the numbers of patients delivered during 1977 to the number of monitors was calculated and the values ranged from 172 to 2708. In nearly 25 per cent of the hospitals it was not possible to monitor all high risk patients. Fetal blood pH estimation was used in conjunction with fetal heart rate measurement in 98 hospitals (40·2 per cent) but 38 (15·6 per cent) had a pH meter in or adjacent to the labour ward although this was not used for pH estimation. Midwives were taught to apply fetal scalp electrodes in half of the units but were taught to collect fetal blood samples in only two. It is suggested that there is a need (i) to improve the monitoring facilities in many units, (ii) to encourage midwives to become more involved in practical monitoring techniques and (iii) to develop improved methods for fetal pH determination during labour.

ELECTRONIC equipment for continuous recording of the fetal heart rate during labour has been available for routine clinical use in the United Kingdom for just over a decade (Huntingford and Pendleton, 1969). During this time it has become generally accepted that this technique reliably detects fetal distress during labour. There is still, however, a lack of agreement whether all patients should be monitored (Edington *et al*, 1975; Lee and Baggish, 1976) or only those who are at high risk (Paul and Hon, 1974; Tutera and Newman, 1975) and also whether or not it is necessary to measure the pH of fetal blood to diagnose fetal asphyxia (Beard *et al*, 1971; Tipton and Shelley, 1971).

The aim of the present study was to investigate the impact of continuous fetal heart rate (FHR) monitoring techniques on clinical practice in the United Kingdom.

METHODS

During September 1978 a postal questionnaire was sent to one consultant at each of 264 Maternity Units in the United Kingdom. The addresses of the Consultant Obstetric Units to which the questionnaires were sent were obtained from the mailing list of the Royal College of Obstetricians and Gynaecologists and the names of the individual consultants from the Medical Directory. A second questionnaire was sent to all non-respondents in mid-October 1978 and the results were analysed in early November 1978.

A telephone enquiry was made to the labour wards of Maternity Units from which the questionnaires were not returned, solely to determine whether or not they possessed any fetal heart rate monitors.

The geographical distribution of the 244 Maternity Units (92·4 per cent) from which replies were received is shown in Figure 1. The total number of deliveries in 243 of these units during 1977 was 480 837; of these 422 894 occurred in England and Wales, 39 688 in Scotland and 18 255 in Northern Ireland. The number of deliveries in England and Wales during 1977 was 568 784, in Scotland 62 350 and Northern Ireland 25 437. These figures were obtained from the Office of Population Censuses and Survey, London, and the Registrar General's Office, Northern Ireland. This survey, therefore, includes 74 per cent of deliveries in England and Wales during 1977, 72 per cent of those in Northern Ireland and 64 per cent in Scotland.

The answers to the following questions were analysed:

1. How many fetal heart monitors do you have in your labour ward?
2. How many of each of the following makes do you possess?
   Sonicaid, Hewlett Packard, Roche, Corometrics, Devices, Other.
3. Which of your patients do you aim to monitor in labour?
   All/High Risk only.
4. Approximately how many of your patients do you monitor in labour?
   10 per cent, 20 per cent, 30 per cent, 40 per cent, 50 per cent, 60 per cent, 70 per cent, 80 per cent, 90 per cent, 100 per cent.
5. Are you able to monitor all your high risk patients in labour?
   Yes/No
6. Do you use your fetal monitors for the antenatal assessment of fetal wellbeing?
   Yes/No
7. Are the midwives in your hospital taught to apply fetal scalp electrodes?
   Yes/No
8. Is continuous fetal heart rate monitoring generally accepted as a reliable means of assessing fetal wellbeing in labour at your hospital?
   Yes/No/Yes, with pH estimation.
9. Do you measure the fetal scalp capillary blood pH in labour when fetal distress is suspected?
   Yes/No
10. Do you have a pH meter in or adjacent to your labour ward?
    Yes/No
11. Are the midwives in your hospital taught to collect fetal scalp blood for pH estimation?
    Yes/No
12. What was the total number of deliveries at your hospital between January 1st and December 31st 1977?

The data were analysed using the SPSS Package available at the University of London Computer Centre. The Chi-squared statistic was used to test for association between the approximate percentage of patients monitored during labour and whether or not midwives were taught to apply fetal scalp electrodes.

RESULTS

Monitoring practice

Only one of the 244 Consultant Obstetric Units, from which the questionnaire was returned, did not have a fetal heart monitor. This was one of the smallest units in the survey, with only 816 deliveries. There were 848 monitors in the remaining 243 units and numbers of each make are shown in Table I. The telephone enquiry to the labour wards of the 20 hospitals from which the questionnaire was not returned established that all these maternity units had fetal heart monitors.

To assess the monitoring facilities available in the labour ward of each maternity unit, the ratio of the number of patients delivered during 1977 to the number of monitors in each labour ward was calculated. This ranged from 172 to 2708 and the distribution of values is

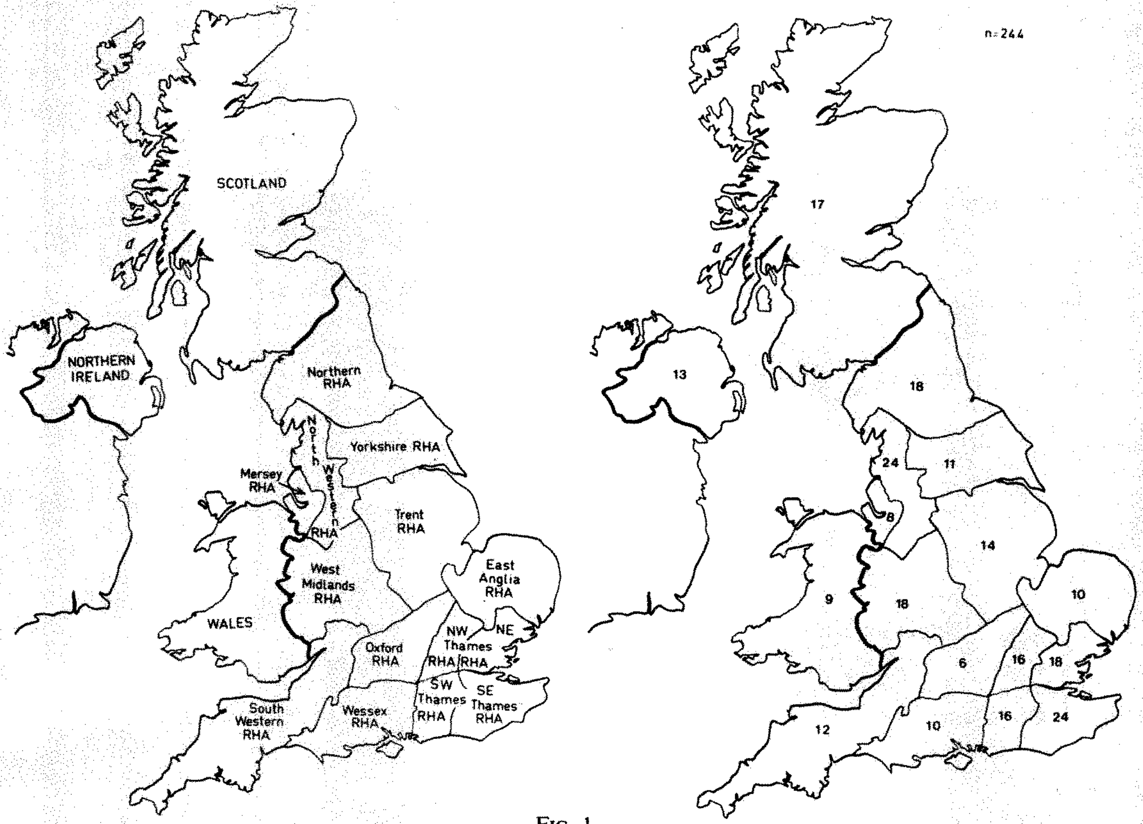

FIG. 1

Geographical distribution of the 244 Maternity Units from which replies were received. England has been subdivided by Regional Health Authorities.

TABLE I

Number of fetal heart monitors of each make used in 243 Maternity Units in the United Kingdom

	Number	Per cent
Sonicaid	592	69·8
Hewlett Packard	229	27·0
Corometrics	12	1·4
Devices	5	0·6
Roche	3	0·4
Other	7	0·8
Total	848	100·0

shown in Figure 2. The use made of these facilities is shown in Figure 3, and the relationship between the available facilities and the extent to which they were used in labour, in Figure 4.

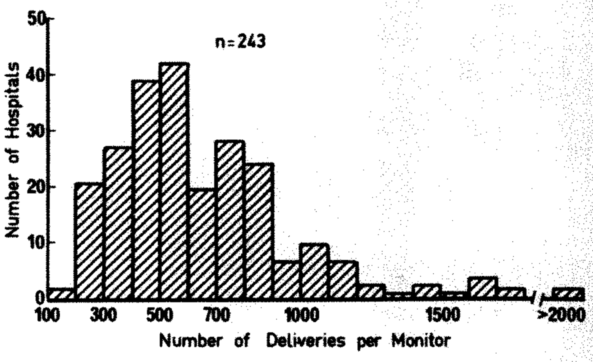

FIG. 2

Histogram of the number of deliveries per monitor during 1977 in 243 Maternity Units in the United Kingdom.

In addition, fetal heart monitors were used for the antenatal assessment of fetal wellbeing in 198 (81·1 per cent) of the units included in the survey.

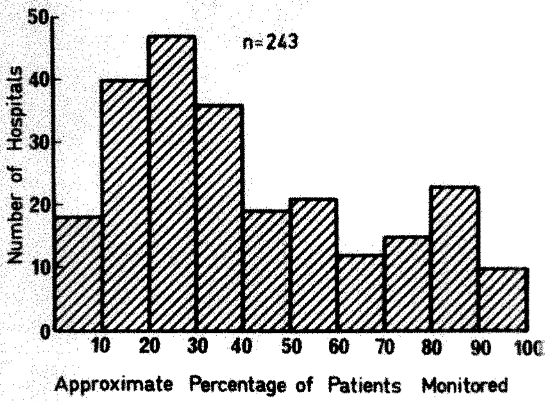

FIG. 3

Histogram of the approximate percentage of patients monitored during 1977 in 243 Maternity Units in the United Kingdom.

Attitudes to continuous FHR monitoring and fetal blood pH estimation during labour

Ninety-one consultants (37·7 per cent) stated that they aimed to monitor all their patients in labour while the remaining 150 (62·2 per cent) monitored only high-risk patients. Despite this, nearly a quarter of the Maternity Units (23·6 per cent) were unable to monitor all their high-risk patients (Table II).

Fetal capillary blood pH estimation was considered to be a necessary adjunct to continuous FHR monitoring by 75 consultants (30·7 per cent), while 147 (64·3 per cent) felt that monitoring alone was generally accepted as a reliable means of assessing fetal wellbeing in labour. Ten consultants (4·1 per cent) stated that these techniques were not generally accepted

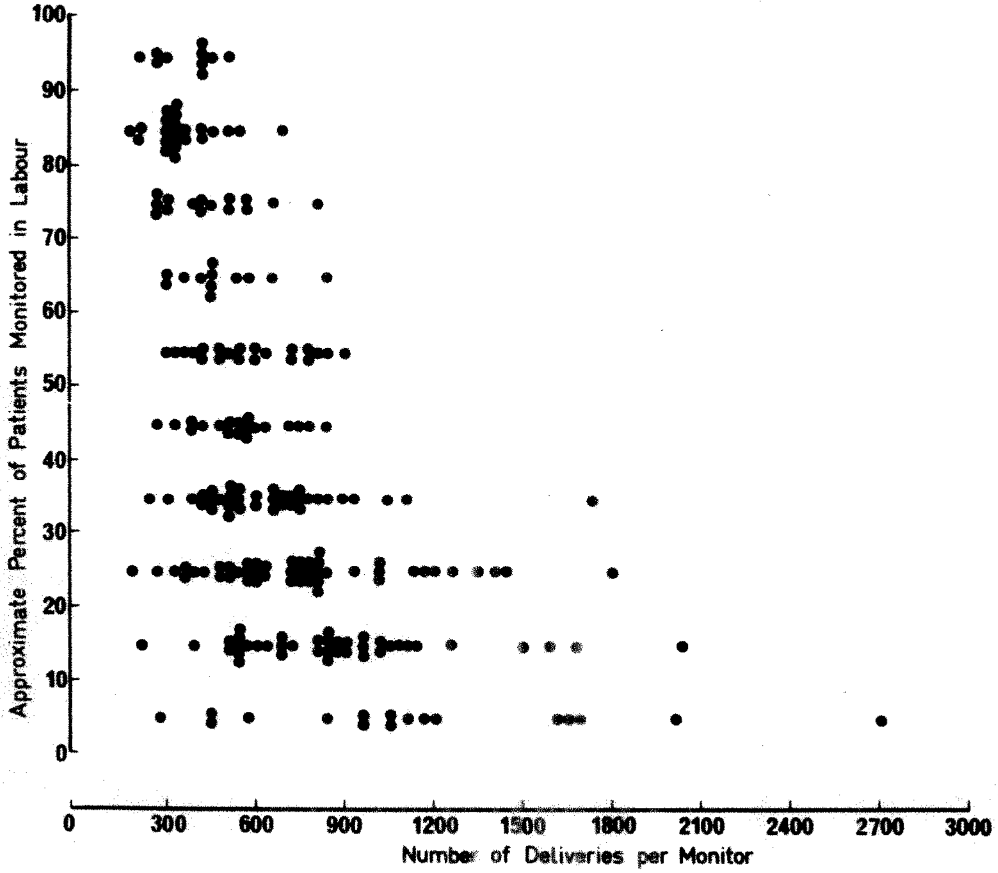

FIG. 4

Scattergram of the approximate percentage of patients monitored in labour plotted against the number of deliveries per monitor during 1977 in 242 Maternity Units in the United Kingdom. (Missing data in one case).

TABLE II

Success achieved in monitoring all high risk patients during labour according to the aim of monitoring in 241 Maternity Units in the United Kingdom. (Missing data in two cases)

Aim of monitoring	High risk patients monitored	
	100%	< 100%
All patients	77 (32·0)	14 (5·8)
High risk only	107 (44·4)	43 (17·8)
Total	184 (76·4)	57 (23·6)

( ) = Per cent of total

TABLE III

Attitudes towards FHR monitoring and fetal pH estimation in 242 Maternity Units in the United Kingdom. (Missing data in one case)

	Fetal pH	
Fetal monitoring	Measured	Not measured
Accepted as reliable	25 (10·3)	132 (54·5)
Reliable with pH estimation	69 (28·5)	6 (2·5)
Not reliable	3 (1·2)	7 (2·9)

( ) = Per cent of total

TABLE IV

Fetal pH estimation and the accessibility of the pH meter in 242 Maternity Units in the United Kingdom. (Missing data in one case)

	pH meter in or adjacent to the Labour Ward	
Fetal pH	Yes	No
Measured	77 (31·8)	21 (8·7)
Not measured	38 (15·7)	106 (43·8)

( ) = Per cent of total

as reliable by the staff working in their hospitals. In practice, however, pH measurements were used in 25 units (10·3 per cent) where the FHR alone was considered reliable and 3 (1·2 per cent) where neither technique was accepted (Table III). In contrast, there were 38 units (15·7 per cent) which had a pH meter in or adjacent to their labour ward but did not use it for fetal pH determinations (Table IV).

Role of the midwife in continuous intrapartum FHR monitoring and fetal blood pH estimation

Midwives were taught to apply fetal scalp electrodes in exactly half of the 244 Maternity Units but were taught fetal blood sampling in only 2 units (0·8 per cent). An analysis of the relationship between the percentage of patients monitored and whether midwives were taught to apply fetal scalp electrodes or not, shows a highly significant association ($\chi^2 = 17{\cdot}96$, $p < 0{\cdot}002$; Table V)—that is more patients were monitored in those units where midwives were taught this technique.

DISCUSSION

The method of data collection used in this survey depended largely on the recall of a single Consultant Obstetrician in each Unit and its accuracy may therefore be questioned. There appeared, however, to be major differences between Units both in the availability of monitors and in the way in which they were used. In addition, there was no general agreement whether all patients should be monitored or only those considered to be at 'high risk'—a division of opinion which is reflected by the bimodal frequency distribution of the percentage of patients monitored in each unit (Fig. 3). One explanation for this difference in attitude may be that while the majority of the studies published to date have shown an improved perinatal outcome in monitored high risk pregnancy compared to unmonitored low risk patients (Paul and Hon, 1974; Tutera and Newman, 1975), there have been very few similar studies where monitoring has been used routinely in all patients (Edington *et al*, 1975; Lee and Baggish, 1976). It is, however, important to note that nearly a quarter of the Units in the survey were unable to monitor even their high risk patients. This appears to have been due, at least in part, to a lack of equipment, but may also have resulted from an inadequate number of labour ward staff and hence limited use of techniques that some may regard as unnecessarily time-consuming. Although the survey did not include any questions about the number of medical and midwifery staff working in each labour ward, it is

TABLE V

Approximate percentage of patients monitored in 241 Maternity Units in the United Kingdom according to whether midwives were taught to apply fetal scalp electrodes. (Missing data in two cases)

Approximate percentage of patients monitored in labour

	≦20	21–40	41–60	61–80	> 80	Total
Taught to apply electrodes	19 (15·6)	38 (31·1)	23 (18·9)	19 (15·6)	23 (18·9)	122
Not taught	39 (32·7)	45 (37·8)	17 (14·3)	8 (6·8)	10 (8·4)	119

( ) = Per cent of row total
$\chi^2 = 17{\cdot}96$; $p < 0{\cdot}002$

of interest that a significantly higher proportion of patients were monitored in those units where midwives were taught to apply fetal scalp electrodes (Table V). This finding may merely reflect a greater interest in monitoring in these hospitals, but it also suggests that more effective use can be made of the available monitoring equipment when the midwifery staff are fully involved in all the practical aspects of fetal monitoring.

There did not appear to be agreement about the value of fetal capillary pH estimation in labour. This procedure was used in 40 per cent of maternity units but a further 16 per cent had a pH meter in or adjacent to their labour ward and did not use it. This suggests that not only is there a lack of enthusiasm for this technique in many units, but that several have tried and rejected it. There is, therefore, a definite need for improved methods of fetal pH determination to be developed in the near future if this potentially valuable method of assessing fetal wellbeing in labour is to achieve wider acceptance.

In conclusion, while this survey demonstrates that there is widespread acceptance of fetal monitoring in most Consultant Obstetric Units in the United Kingdom, there appears to be great variation in the way in which the technique is used in clinical practice. In addition, it appears that there is a need (i) to improve the facilities available in many units, (ii) to encourage midwives to become more involved in practical fetal monitoring procedures and finally (iii) to develop improved methods of fetal pH determination during labour.

ACKNOWLEDGEMENTS

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DETECTION OF FETAL RISK IN POSTMATURITY

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Summary

Ninety-seven postmature pregnancies were monitored by amnioscopy or amniocentesis (to determine presence or absence of meconium), oxytocin challenge tests (OCT), 24-hour urinary oestriol estimations and fetal movement counts. The colour of the amniotic fluid and the result of the OCT predicted almost all cases of fetal distress in labour and infants with low Apgar scores. Oestriol estimations and fetal movement counts predicted fetal distress only when combined with other positive tests. Of 50 patients with no abnormal test results, 49 had uneventful labours. The Caesarean section rate was not above average and all babies were liveborn.

THERE is controversy about the management of postmature pregnancies. Some do not recognise them as a clinical problem (Evans *et al*, 1963; Brown, 1957), and others advocate induction at 41 to 42 weeks (Browne, 1963; Mathews, 1967).

The majority now believe that postmaturity endangers the fetus. Placental function may be impaired (Walker, 1954; Mathews, 1967), the volume of amniotic fluid may be diminished, and the mean weight of the baby may be increased (Beischer *et al*, 1969; Frampton and Clayton, 1968). Some have reported a two-to three-fold increase in perinatal mortality rate compared to term deliveries (Gibson ,1955; Browne, 1963), an 11 to 33 per cent incidence of fetal distress during labour compared with 7 to 18 per cent in term deliveries and a two- to five-fold increase in the number of obstetric interventions (Schneider *et al*, 1978; Beischer *et al*, 1969).

We are against routine induction of labour at an agreed gestational age as an answer to postmaturity and preferred a more logical and scientific approach. We therefore designed an investigation to test a practical and rational scheme for the management of postmaturity.

PATIENTS, MATERIALS AND METHODS

We define postmaturity as a pregnancy which goes beyond 273 days from the date of ovulation (41 weeks of amenorrhoea). Only women in whom the date of ovulation was certain from a basal body temperature chart or who had a positive pregnancy test within six weeks of the last menstrual period were included in this study. Patients with complications such as maternal hypertension, apparent fetal growth retardation and diabetes were excluded.

Four main methods of examination were

employed in the 97 patients who were left in our study: a search for brown, green, yellow or grey discolouration of the amniotic fluid by amnioscopy (or amniocentesis), the oxytocin challenge test (OCT), 24 hour urinary oestriol estimation by the fluorometric method of Ittrich (1962) and fetal movement counts.

Oxytocin challenge test (*OCT*)

After 20 minutes of non-stressed external cardiotocographic recording, patients were started on 2 milliunits of oxytocin/minute by Ivac infusion pump. The dose was doubled every 20 minutes to a maximum of 32 milliunits/minute until three uterine contractions were observed in two consecutive 10-minute periods at which point the OCT was considered complete. The OCT was considered (i) negative if there were no late decelerations, (ii) positive if there were late decelerations with three or more consecutive uterine contractions and (iii) suspicious if there were intermittent late decelerations, persistent baseline bradycardia or tachycardia, reduced baseline variability or repeated variable decelerations.

Fetal movement count

Patients were asked to count the number of fetal movements that they felt during a one-hour period in the morning and evening and the results were expressed as a daily mean.

The amnioscopy and OCT were done consecutively on the morning of admission to hospital. If both were positive a Caesarean section was performed unless the condition of the cervix was very favourable for induction, in which case, patients had an amniotomy and oxytocin infusion.

If either the amnioscopy or OCT was positive, patients were induced by amniotomy and oxytocin infusion.

If both the amnioscopy and OCT were negative, the patient was sent home for 48 hours during which time a 24-hour urine collection was made and fetal movements were counted. If spontaneous labour had not intervened, the cycle of examinations was repeated.

If the OCT was suspicious and the amnioscopy negative, the OCT was repeated after 24 hours. Three consecutive suspicious OCTs were regarded as positive.

Urinary oestriol levels and fetal movement counts did not influence the decision to induce labour. All patients were continuously monitored during labour and careful records were kept of the infant's Apgar score at one and five minutes and its subsequent progress while in hospital.

Fetal distress was diagnosed if there was meconium staining of the amniotic fluid and/or persistent late decelerations of the fetal heart rate during labour.

TABLE I

Summary of data

Patients—total	97	
Nullipara	38	(38·2%)
Age (years) 15–20	12	(12·4%)
21–25	48	(49·6%)
26–35	35	(36·1%)
> 35	2	(2·1%)
Examinations		
Amnioscopy	270	
Negative	256	
Positive	14	
Amniocentesis (because amnioscopy impossible)	3	
Negative	1	
Positive	2	
Oxytocin challenge test	297	
Negative	286	
Positive	6	(2·0%)
Suspicious	5	(1·7%)
Urinary oestriol determinations	165	
Low (< 8 mg/24 hour)—patients	15	(15·5%)
Drop (> 50%)—patients	4	
Fetal movement count		
Movements counted	28424	
Hours counted	836	
Mean movements/hour	34	
Mean daily count low (< 15/hour)—patients	16	(16·5%)
Labour		
Spontaneous	77	
Induction	19	(19·6%)
Elective Caesarean section	1	
Fetal distress	23	(23·6%)
Late decelerations FHR patterns	6	
Meconium in amniotic fluid	13	
Late decelerations + meconium	4	
Mode of delivery		
Normal delivery	85	(87·6%)
Vacuum extractions/forceps	5	(5·1%)
Caesarean section	7	(7·2%)
Nonprogressive labour	2	
Slow progress + fetal distress	2	
Severe fetal distress	2	
Positive OCT + meconium	1	

TABLE II

The incidence of fetal distress and low one-minute Apgar scores according to individual parameters examined

	Positive amnioscopy	Oxytocin challenge test		Mean daily fetal movement count less than 15/hour	24-hour urinary oestriol less than 8 mg	Drop of 24-hour urinary oestriol level of more than 50% below previous value	No abnormal findings
		Positive	Suspicious				
Total	16	6	4	16	15	4	50
No fetal distress	—	1	1	9	13	1	49
Fetal distress with;							
one-minute Apgar score 7 or more	13	3	0	6	—	1	1
one-minute Apgar score less than 7	3	2	3	1	2	2	—

RESULTS

Table I summarises some clinical data and overall results. Ninety of the 97 patients had one to four examinations of amniotic fluid colour, five had five examinations and the remaining two, six and seven examinations, respectively. There were no fetal or maternal complications. The 14 patients with positive amnioscopies and 2 with positive amniocentesis all had meconium when the membranes were ruptured shortly after examination. Similarly, meconium was not seen at membrane rupture within 48 hours of a negative amnioscopy or amniocentesis.

Six OCTs (2 per cent) were positive and labour was induced immediately. Five tests were classified as suspicious and in four of these patients, spontaneous labour started within 24 hours. The remaining suspicious test became positive when repeated. Taking into account only the last OCT before induced or spontaneous labour, there were six positives (6·2 per cent), four suspicious (4·2 per cent) and 87 negative results. Of the six patients with positive OCTs, five had late decelerations during labour and one was regarded as a false positive test. Three of the four suspicious OCTs were associated with repeated late fetal heart rate decelerations during labour. Only two patients (2·3 per cent) of the 87 with negative OCTs within 48 hours of labour developed abnormalities of the fetal heart rate during labour.

Tables II and III relate the results of amnioscopy or amniocentesis, OCTs, urinary oestriols and movement counts to the condition of the fetus during labour and immediately after delivery.

There were 50 patients in whom all tests were negative and in only one of them did fetal distress develop during labour. There were 47 patients in whom at least one test for fetal well-being was positive (or abnormal) and in 22 of them there was fetal distress during labour, including all nine of those with more than one positive test.

Twenty-three patients showed a positive or suspicious OCT and/or a positive amnioscopic examination before labour and 21 of them had fetal distress during labour.

There were also 23 patients with an oestriol drop, a low oestriol or decreased fetal movements as single positive tests and none of them developed fetal distress in labour.

There were no intrauterine fetal deaths. One baby died a short time after a spontaneous delivery accompanied by fetal distress. A post-mortem examination revealed dyschondroplasia and hypoplastic lungs. Seven infants developed physiological jaundice.

Table IV shows the distribution of birth weight by week of gestation and also the incidence of fetal distress in the various birth weight ranges. There was no increase in the incidence of large babies with an increasing gestational age and the incidence of fetal distress was very similar in all

TABLE III

The incidence and type of fetal distress in labour, low one-minute Apgar scores and mode of delivery according to findings at the last examination before labour in 97 cases of postdate pregnancy

	Last examination before labour				Fetal distress				
No. of patients	OCT*	Amnioscopy*	Oestriol	Fetal movements	Late decelerations only	Meconium only	Late decelerations +meconium	Mode of delivery other than normal	One-minute Apgar score less than 7
1	+	+	Drop Low	Low	—	—	1	Forceps	1
1	+	+	Drop Low	N	—	—	1	CS	1
1	+	—	N	Low	1	—	—	CS	—
1	S	+	N	N	—	—	1	VE	1
4	—	+	N	Low	—	3	1	1CS	—
3	+	—	N	N	2	—	—	1VE	—
3	S	—	N	N	2	—	—	1CS	2
9	—	+	N	N	—	9	—	2VE 1CS	—
1	—	—	Drop	Low	1	—	—	—	—
1	—	—	Drop	N	—	—	—	—	—
13	—	—	Low	N	—	—	—	—	—
9	—	—	N	Low	—	—	—	—	—
50	—	—	N	N	—	1	—	1CS	—

*S = suspicious, + = positive, — = negative, N = normal; CS = Caesarean section; VE = vacuum extraction.

TABLE IV

Distribution of fetal weight according to the week of delivery. The incidence of fetal distress in the various weight groups is indicated

Birth weight (g)	Week 42	Week 43	Week 44+	Fetal distress	
				No.	per cent
2500–2999	3	5	—	2	25
3000–3499	19	22	4	17	22·6
3500–3900	14	14	2		
4000–4499	9	2	—	4	28·6
4500+	2	1	—		
Total	47	44	6	23	23·6

birth weight groups. One cannot therefore blame the fetal distress on mechanical problems. Twelve of the 14 newborn weighing 4 kg or more were delivered normally, one by vacuum extraction and one by Caesarean section for failure to progress in labour.

DISCUSSION

Most investigators have reported an increased perinatal mortality with postmaturity but others (Magram and Cavanagh, 1960, Schneider *et al*, 1978) no difference between term and post-term deliveries. Only Schneider *et al* (1978) had a range of placental function tests available and the ability to continuously monitor the state of the fetus during labour. The data presented in our study suggest that judicious application of tests of placental function and fetal monitoring may help to reduce perinatal mortality and morbidity in postmaturity to a minimum without overtaxing the resources of the average obstetric service. These measures detect patients' cases needing intervention and also eliminate unnecessary inductions of labour. For these purposes the OCT and examinations for the detection of meconium appear to be the most useful, being reliable, rapid and highly predictive of fetal distress.

The place of urinary oestriol estimation and fetal movement counts are in the management of postmaturity less clear. A low oestriol, oestriol drop or decreased fetal movements were not helpful when occurring alone but when detected in combination with another abnormal test provided confirmation of placental insufficiency.

Other studies have also shown a poor correlation between oestriol excretion, fetal distress in labour, condition of the infant at birth and a positive OCT (Frampton and Clayton, 1968; Schneider *et al*, 1978). The value of serum oestriol assays remains to be determined (Miller *et al*, 1977). The OCT has probably replaced urinary oestriol estimation in identifying fetuses who are at risk of intrauterine death or severe perinatal morbidity, at least in cases of postmaturity.

We disagree with those who have stated that cephalopelvic disporportion is the only or chief problem (Clayton, 1941). Although the proportion of large babies was high compared to term deliveries, a large birth weight did not apparently influence the incidence of fetal distress, the incidence of delay in labour or the incidence of section.

On the strength of the results of this study, we now manage postmaturity by observation of amniotic fluid colour and OCTs every 48 hours. Although the value of fetal movement count is uncertain, we instruct patients to report for reassessment if they experience less than 10 movements/hour.

The performance of an OCT every 48 hours in a relatively large number of patients may present problems but is recommended because of reports of fetal death within one week of a negative OCT (Evertson *et al*, 1978). We are at present investigating the value of a non-stress test and the performance of an OCT every four days in cases of suspected postmaturity.

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DYNAMIC FETAL CEPHALOMETRY

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Summary

An iterative method of fetal cephalometry for use with real time scanners is described using a flow chart. The method is shown to be capable of yielding measurements having a standard deviation of less than 1 mm and we have found it to be superior to the combined A and B scan technique from which it is derived.

IN a previous study (Davies and Richardson, 1976) we described a dynamic method of fetal cephalometry and presented a detailed description, with a flow chart, of a modification of Campbell's combined A and B scan technique (Campbell, 1968). This technique was extended to include a method of checking the fetal cephalic diameter by rotating the scanning plane through a right angle after making an acceptable measurement. The advent of real time ultrasound apparatus led us to re-evaluate fetal cephalometry using such machines and the outcome is now presented.

MATERIALS AND METHODS

Two real time ultrasound scanners, one manufactured by Philips and the other by ADR, were compared to the Diasonograph 4200 used in the department of Radiology at the City Hospital, Nottingham. Informed consent was obtained from patients attending for cephalometry for three measurements to be made on each of the three machines. For every measurement a note was made as to whether the image criteria were poor, good or excellent. Poor image criteria corresponded to those described previously (Davies and Richardson, 1976), namely a relative short midline with an incomplete skull outline. Good criteria consisted of a continuous midline bisecting the head which showed a complete circumference except in the coronal plane. Excellent criteria consisted of a discontinuous midline, but the discontinuity was only a short gap bounded on either side by parallel lines. Each set of three measurements was timed and when all nine results had been obtained the patient was asked with which machine she preferred to be examined.

Method of cephalometry

The combined A and B scan technique could not be employed with the real time ultrasound scanners we used as they did not have an A scan display. However, the iterative technique described here has the advantage that it does not require an A scan.

Since positional information is not necessary for real time scanning, movement of the probe is not constrained by a co-ordinate measuring system and the probe can be placed on the maternal abdomen at any angle. Therefore, in order to describe the movement of a real time probe, it is necessary to define a unique set of co-ordinate axes and Figure 1 shows the definitions that were adopted in this study. Axis 1 is the longitudinal axis of the transducer and since movement about this axis is the easiest angulation to perform it is referred to as angle +

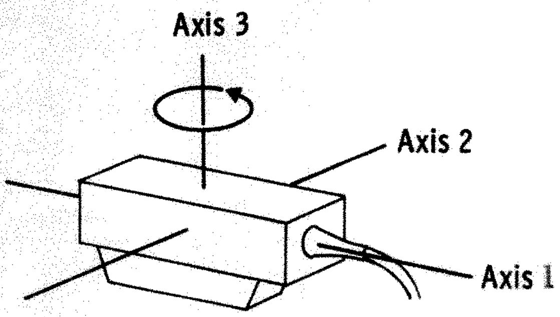

FIG. 1
Coordinate axes used for fetal cephalometry with real time scanners. For detailed description see text.

or angle −. Axis 2 is the transverse axis through the centre of the probe and angulation about this axis is designated angle long + or angle long − since it is the longitudinal axis that moves when the probe is rotated about axis 2. Axis 3 is the axis at right angles to both axis 1 and axis 2 through the centre of the probe and movement about this axis is described as rotation.

A flow chart of our revised technique for cephalometry is shown in Figure 2 with the measuring cycle on the left and the checking cycle on the right. Figure 2 and Figure 3 together describe and illustrate the procedure in a formal manner, but in practice the steps may be inter-

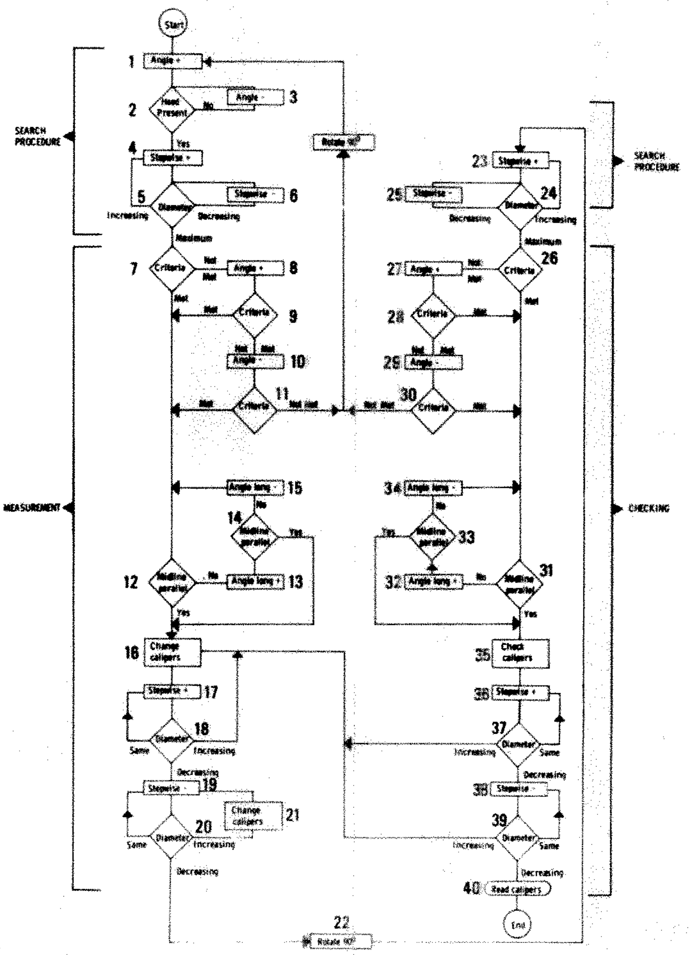

FIG. 2
Flow chart of method for fetal cephalometry.

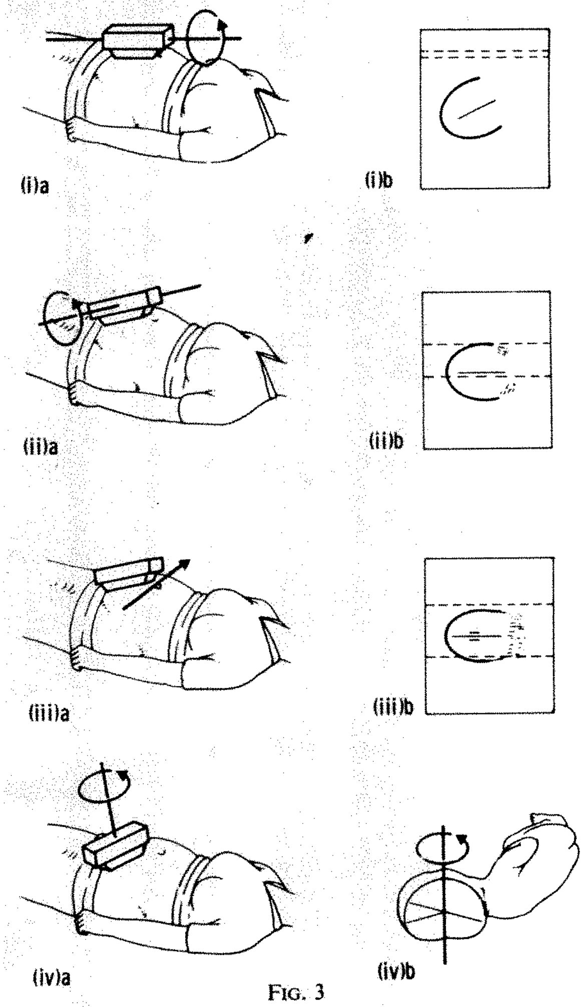

FIG. 3

The transducer positions and corresponding images used in this method for cephalometry. (i) The search procedure, steps 1 to 6 in the flow chart. (ii) The second sub-routine, steps 12 to 15 adjusting the probe to bring the midline parallel to the probe face, the distal marker is used to check this. (iii) The maximum diameter of the head is found by a translational movement and the calipers set up on the leading edges of the skull echoes at the maximum diameter, steps 16 to 21. (iv) Rotation of the probe through 90°, step 22. (iv)b The maximum cephalic diameter is shown as as unique diameter at the intersection of the two planes.

changed or carried out simultaneously rather than sequentially. A cephalic presentation is assumed in describing the method but the technique is equally valid for other presentations.

The probe is placed on the maternal abdomen so that axis 1 lies along the longitudinal axis of the patient. The position of the fetal head is determined by angling the probe about axis 1 (steps 1 to 3) as shown in Figure 3 (i)a. Figure 3 (i)b illustrates the type of image obtained though the angulation has been exaggerated for clarity. Obviously the picture varies depending on the position of the fetus and whether the cable end of the probe is pointing towards the patient's head or feet.

Once the head has been located the probe is moved so that it is positioned over the maximum diameter (steps 4 to 6). The operator has now completed the search procedure and must check whether or not the image fulfils the criteria mentioned above before making a measurement. The probe is angled about axis 1 to find the largest diameter with the best criteria, namely a continuous midline with a complete outline of the skull (steps 7 to 11). It should be noted that with our method we make a measurement in the initial scanning plane and, therefore, the first measurement is made in the fetal coronal plane. In this plane the base of the skull may be seen and the smooth ellipse of the calvarium is completed by an irregular line (Fig. 3 (ii)b). At this point it is most unlikely that the midline is parallel to the surface of the probe. To rectify this situation the probe is rotated about axis 2 as shown in Figure 3 (ii)a (steps 12 to 15). It may even be necessary to lift one end of the probe off the abdomen to obtain the correct image. The calipers are now positioned on the leading edges of the skull echoes (step 16). If the calipers are bar calipers, the distal bar can be used to check if the midline is parallel to the probe face as the bar is moved across the head to the distal skull echo (Fig. 3 (ii)b). The probe is now moved along axis 2, keeping the angulation constant, in order to check that the diameter measured is in fact the maximum (Fig. 3 (iii)a; steps 17 to 21). If the criteria are excellent the picture obtained in the coronal plane is as shown in Figure 3 (iii)b.

The probe is now rotated through 90° about axis 3 (step 22; Fig. 3 (iv)a) and the measurement checked. The line of maximum cephalic diameter is at the intersection of two planes (Fig. 3 (iv)b) and the same result should be obtained when measured in each plane. A dextrous operator can, in suitable circumstances, rotate the probe with axis 3 along the line of maximum cephalic diameter which reduces the time needed to complete a measurement but this, fortunately, is not essential to the success of the operation.

We have already noted that in this first part of the procedure the transducer and its curtain of ultrasound lies in the fetal coronal plane and the rotation now aligns the transducer in a plane parallel to the transcoronal plane which is the plane selected for measurement in the B scan method.

The checking cycle is merely a repetition of the measuring cycle in another plane and this is illustrated in Figures 4 (v) to (vii) (steps 23 to 40). The head shown in Figure 4 (v)b is angled so that it lies obliquely across the axis of the maternal pelvis. To bring the midline parallel to the transducer face the transducer must be rotated about axis 2.

If the measurement is identical to that obtained previously the reading is accepted but if the calipers need adjustment a further check must be made. The calipers are readjusted to the new separation; the probe is rotated through 90° and the checking cycle repeated. This process is continued until two identical measurements are obtained in two planes at right angles.

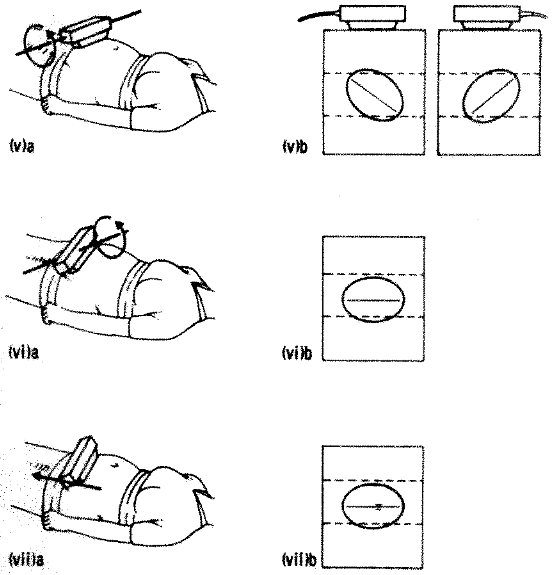

FIG. 4

The checking procedure. (v) The first sub-routine of the checking procedure, steps 26 to 30. (v)b Reversing the probe gives a reversed image and angulation must be in the opposite sense. (vi) Angulation of the probe brings the midline parallel to the caliper bars (and transducer face). (vii) The maximum is again found, if the caliper separation has to be altered the checking procedure must start again having rotated the probe back through 90°.

RESULTS

We examined 24 patients and made three sets of three measurements on each patient, that is three measurements of the fetal cephalic diameter were made on the Diasonograph, then three on the Philips and finally three on the ADR. For every patient the mean and the variance were calculated for each machine and also the mean and the variance of the machine means, this last mean being termed the grand mean. The grand mean and its variance and the individual machine variances are shown in Table I. It would be expected that the variance of the grand mean would be of the same order or smaller than the individual machine variances and this was the case apart from patient No. 9.

For each machine the pooled variance was calculated and this showed that the ADR had the smallest variance and the Diasonograph the greatest. Bartlett's test for the homogeneity of the variance was applied as advocated by Docker and Settatree (1977) and for each machine the variance was found to be homogeneous.

To discover if there was any significant difference between the machines the F-test was applied to the ratios of the pooled variances with 23,23 degrees of freedom. In each case the ratio indicated that the differences between the machine variances were not significant.

The differences between means were then calculated for all three machine pairs on every patient to ascertain if there was any difference between machine means. The results were summed for each pair of machines and the mean difference, variance and standard deviation calculated. The results are presented in Table II from which it can be seen that there is a significant difference between the Diasonograph and the ADR but not between the Diasonograph and the Philips or the Philips and the ADR. The mean difference between the Diasonograph and the ADR was 0·8 mm ($0{\cdot}005 > P > 0{\cdot}001$).

When a measurement was made a note was taken of whether the criteria were poor, good or excellent. Assigning 1 point for poor criteria, 2 for good and 3 for excellent, a score was obtained for each set of three measurements. A

TABLE I

Ultrasound measurements of fetal cephalic diameter (in mm) using three different machines

	Diasonograph		Philips		ADR		Grand Mean	
Patient	Mean	Variance	Mean	Variance	Mean	Variance	Mean	Variance
1	93·0	0·16	93·7	0·33	92·5	0·93	93·1	0·34
2	92·4	2·36	94·3	0·33	91·7	0·31	92·8	1·85
3	88·4	1·70	88·7	0·33	88·9	0·46	88·7	0·06
4	87·0	1·72	87·7	2·33	87·2	0·32	87·3	0·12
5	80·3	0·09	79·0	1·00	79·4	1·04	79·6	0·44
6	74·5	0·61	74·0	1·00	73·6	0·26	74·0	0·22
7	74·8	8·62	71·7	0·33	72·8	0·52	73·1	2·57
8	71·8	3·45	73·0	1·00	69·7	0·41	71·5	2·86
9	71·9	1·84	71·7	0·33	69·4	0·42	71·0	1·93
10	69·8	1·46	70·3	0·33	69·1	0·56	69·7	0·36
11	68·3	0·14	68·3	2·33	69·5	0·04	68·7	0·48
12	68·4	0·65	68·3	0·33	68·0	0·13	68·3	0·05
13	67·2	0·33	68·3	2·33	67·3	1·74	67·6	0·39
14	68·4	2·36	67·7	0·33	65·6	0·57	67·2	2·02
15	59·0	2·50	59·0	1·00	59·6	0·22	59·2	0·10
16	58·7	0·50	58·7	1·33	57·3	0·10	58·2	0·69
17	57·0	2·92	54·7	1·33	55·1	1·40	55·6	1·60
18	53·5	2·01	53·0	4·00	53·5	0·57	53·3	0·08
19	46·6	2·30	46·0	1·00	46·2	0·34	46·3	0·10
20	46·7	0·42	45·0	1·00	45·3	0·41	45·7	0·78
21	43·9	0·60	43·0	1·00	42·1	1·42	43·0	0·87
22	37·1	1·96	36·0	1·00	38·2	9·72	37·1	1·21
23	33·8	0·49	33·3	0·33	33·6	0·22	33·6	0·06
24	33·4	5·32	30·7	2·33	32·5	0·44	32·2	1·93
Pooled variance		1·86		1·13		0·94		0·88
Bartlett's Test		25·5		14·7		33·6		32·4

TABLE II

Differences of means

	Diasonograph and Philips	Philips and ADR	Diasonograph and ADR
Total	10·23	8·03	18·27
Mean	0·43	0·34	0·76
Variance	1·50	1·92	1·19
t-test	1·71	1·18	3·42
			0·005 > P >0·001

score of 3 indicated three poor measurements and a score of 9, three excellent measurements. The total score for all 24 patients, the mean score and the range of scores are given in Table III. The ADR and the Philips had an identical mean score with the Diasonograph slightly smaller.

The length of the examination was not recorded for every patient but Table IV gives a summary of the available data. The Philips and the ADR were very quick to use and the Diasonograph much slower. The differences between the mean times were not significant for the Philips and the ADR but were significant for the

TABLE III

Summary of the scores for the image criteria

	Diasonograph	Philips	ADR
Total score	168	179	179
Mean	7·00	7·46	7·46
Range	4–9	3–9	4–9

TABLE IV

Length of time required for ultrasound examination

	Duration of examination (minutes)		
	Diasonograph (n = 17)	Philips (n = 21)	ADR (n = 20)
Mean	7·2	3·7	4·8
Variance	7·90	1·13	3·22
SD	2·81	1·06	1·79

Diasonograph and Philips ($P<0·001$) and the Diasonograph and the ADR ($0·01>P>0·005$).

The patients were hesitant about commenting on which machine they preferred. Six preferred the Philips, 2 of them preferred the image obtained on another machine (1 the Diasonograph and 1 the ADR) though they found the Philips probe with the contour cushion more acceptable. Four patients liked the ADR and four the Diasonograph; the remaining patients had no preference or did not wish to comment.

DISCUSSION

After the publication of our previous paper (Davies and Richardson, 1976) we have had various comments about our use of a flow chart as a descriptive device. Some have maintained that it makes the method more difficult to understand and others that that degree of formalisation is unnecessary. A detailed verbal description of the method is long and tedious and perhaps this is why other authors have referred to 'the combined A and B scan method' or 'a modification of Campbell's method'. We believe that it is important to specify exactly the steps necessary to make a measurement so that operators can be sure they are following the same method. This necessitates a high degree of formality in the description but is a help when results are compared.

A flow chart formalises the process and it is particularly useful for checking that the exact procedure is being followed when teaching the method. This formal description segregates the process into various sub-routines and identifies accurately and separately movements of the transducer, changes in the caliper position or settings and decisions to be made. When flow charts of different methods are available it is easy to count the number of steps (rectangles) decision points (diamonds) and pathways (lines) and compare the complexity of the methods. This comparison shows that fetal cephalometry by a real time method involves more steps despite eliminating the steps involved in making a scan and checking a B scan necessary when using a B scanner. The reason for this increase in complexity is that it is not possible to measure angles with a real time probe and, therefore, it is necessary to assess the correct angulation by observing the signs in the fetal head. This implies that the whole procedure of the combined A and B scan method is run through when making or checking a measurement using a real time scanner. Using our present method of fetal cephalometry for real time scanners and the method for static B scanners described previously (Davies and Richardson, 1976) we found differences between the two types of machine, the variance of the measurements made with the real time scanners being lower than the variance of the Diasonograph measurements. Although none of the differences between the variances was significant, the ratio for the Diasonograph and the ADR was just smaller than the value of the F distribution at the 5 per cent level (23,23 degrees of freedom).

The most important differences between real time and B scanners is the difficulty of detecting fetal motion with a static scanner. The pictures obtained with a static scanner give an appearance of constancy to the uterine contents which is quite misleading. Occasionally one can see two images on the B scan, if the head moves during the time taken to make a scan over it but, more often, movement can only be detected using the A scan. Under these circumstances it is possible to record a fetal head diameter measurement which does not fulfil the required criteria although the operator is unaware of this.

The movement of a suspended measuring frame is awkward and in the best hands results in an error of up to 5° (the smallest possible movement of the Diasonograph measuring frame). Using other equipment, for example the Kretz Combison (Docker and Settatree, 1977) or the Picker 102, the error may be greater and in some cases it may be impossible to measure the angles properly (Docker and Settatree, 1977) although this is an integral part of the method (Campbell, 1968).

There was a significant difference between the mean of measurements obtained on the Diasonograph and those obtained on the ADR, the ADR measurements being generally smaller than the Diasonograph measurements. The reasons for this are possibly that with a static scanner the ultrasound beam can only be aligned perpendicular to the fetal skull by eye. If the beam is non-perpendicular, the measured diameter will be greater than the actual diameter. With bar calipers on real time scanners it is easier to ensure that the measurement is made with the midline perpendicular to the ultrasound beam.

It was generally easier to obtain good criteria with the real time scanners in a significantly shorter time both of which probably contributed to the decreased variances of the real time measurements. Investigations with real time scanners can be completed more quickly than with B scanners because, with the former, it is not necessary to spend time building up a static scan as the presentation of the image is instantaneous and continuous, B scanning is slower because there are two oscilloscopes carrying different information to the observer and the eyes need to move from one to the other while the brain integrates the information. Measuring and estimating the various angles required in B scanning is also time consuming and a further source of information to be passed from eye to brain and assimilated. Real time scanners do not have any of the above disadvantages, the only drawbacks being decreased resolution for the same frequency and increased incidence of artefacts and reverberation echoes in the fetal skull.

Some operators are unduly restricted in their movements when using real time scanners. They tend to hold the transducer in either longitudinal or transverse positions on the maternal abdomen. It is essential however, for the checking procedure to move the transducer plane through 90° with respect to the fetal head and this is rarely along the longitudinal or transverse maternal axis or necessarily parallel to a tangent to the maternal abdomen.

TABLE V

Comparison of variances

Present Study	Diasonograph	Philips	ADR
Variance	1·86	1·13	0·94
SD	1·36	1·06	0·97
Docker and Settatree (1977)		Kretz	ADR
Op. 1 Variance		2·28	1·47
SD		1·57	1·21
Op. 2 Variance		5·56	1·78
SD		2·36	1·33

Table V compares our results with those of Docker and Settatree (1977). The values obtained in our study are smaller than those of Docker and Settatree (1977) and in our opinion are evidence of the superiority of the iterative method over the single pass method. During measurement it is often necessary to make several passes over the fetal head before two results that check can be obtained. The translational movement necessary to check that one is at the maximum diameter of the fetal head is more difficult with real time scanners than B scanners though angulation is easier. Rotation of the transducer for the checking procedure is very important in minimising errors due to this problem.

CONCLUSION

Real time scanners have several advantages over B scanners for cephalometry, namely speed, simplicity and accuracy. The operator can continuously view a single image and rapidly obtain a measurement without an A scan.

Using our modified iterative technique for real time scanners it is possible to obtain results that are as reliable as those produced using the combined A and B scan technique with a B scanner. In addition, our real time results are probably less variable than B scan measurements.

ACKNOWLEDGMENTS

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AMNIOTIC FLUID OPTICAL DENSITY DETERMINATION AS A RAPID TEST FOR ASSESSMENT OF FETAL LUNG MATURITY

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Summary

The lecithin/sphingomyelin (L/S) ratios and optical densities at 650 nm were determined for 158 samples of amniotic fluid obtained by amniocentesis. A further 24 samples collected by vaginal aspiration from patients with spontaneous rupture of the membranes were also analysed. The relation between the L/S ratio and the optical density suggests that the more rapidly obtainable optical density measurement could be used as a screening procedure for fetal pulmonary maturity. A valid estimate of maturity by optical density is not possible in amniotic fluid aspirated from the vagina.

THE measurement of the lecithin/sphingomyelin (L/S) ratio is a relatively sophisticated and time-consuming laboratory procedure. Although in clinical practice this test has proved to be reliable, there is still a need for a more convenient and rapid estimate of fetal pulmonary maturity. Clements *et al* (1972) proposed the 'shake test' as an alternative measurement of surfactant lecithin, but although both simple to perform and more rapid than the L/S ratio test, the 'shake test' has met with considerable criticism.

Recently, Sbarra *et al* (1977) and Copeland *et al* (1978) have reported on the correlation between the optical density of amniotic fluid and the L/S ratio. Sbarra *et al* (1977) showed that the optical density of amniotic fluid at 650 nm reliably predicted an L/S ratio of two or more in 98 per cent of the samples analysed, and proposed that it could be considered as another index of fetal maturity. Arias *et al* (1978) have also investigated this proposed test and concluded that it was not an acceptable substitute for L/S ratio in the assessment of fetal pulmonary maturity.

These conflicting views suggested the need for further study.

METHODS

A total of 158 samples of amniotic fluid was obtained from 134 patients by amniocentesis. In addition, 24 samples were obtained by vaginal aspiration from patients with spontaneously ruptured membranes.

The clinical indications for amniocentesis are shown in Table I.

All samples which were obviously contaminated with blood or meconium were excluded from this study. As soon as a sample was re-

TABLE I

Indications for amniocentesis

Reasons for amniocentesis	Number	Per cent
Hypertension/pre-eclampsia	50	31·6
Intrauterine growth retardation	52	32·9
Rhesus incompatibility	21	13·3
Diabetes mellitus	19	12·0
Ante-partum haemorrhage	3	1·9
Hydramnios	4	2·5
Uncertain gestational age	9	5·7
	158	99·9

ceived, it was centrifuged for 10 minutes at 900 *g* and the optical density was determined in a Unicam SP600 Spectrophotometer, with appropriate red filter, at 650 nm, using 1 cm cells with distilled water as blank.

L/S ratios were determined routinely by a modified Gluck procedure, but using 'Merck' thin-layer chromatographic (TLC) plastic sheets coated with silica and stained with phosphomolybdic acid/stannous chloride (Wagstaff *et al*, 1974); L/S ratios were estimated planimetrically. An L/S ratio of 2 was taken to indicate fetal pulmonary maturity and in this series no false positive results were observed.

RESULTS

The relation of the L/S ratio to optical density at 650 nm in the 158 samples obtained by amniocentesis is illustrated in Figure 1. The terms in the four sectors of Figure 1 are defined thus (Sbarra *et al*, 1977): (i) immature—L/S ratio <2, optical density <0·15; (ii) mature—L/S ratio >2, optical density >0·15; (iii) false-negative—mature by L/S ratio, immature by optical density; (iv) false-positive—immature by L/S ratio, mature by optical density.

The average line falls on a hyperbola. When reciprocal L/S ratio was plotted against reciprocal optical density, a straight line was obtained (r = 0·69).

When transposed into the direct plot, L/S ratio versus optical density, this line produced the hyperbola of Figure 1.

For the amniocentesis samples, two false-positive results were obtained for an optical density cut-off of 0·15 (Table II) and both samples were from patients with pre-term fetuses (36 and 37 weeks). They provide some ground for suggesting that a cut-off level greater than 0·15 be used.

Eleven false-negative results were obtained from amniocentesis samples, four of which were from diabetic patients. Such low levels of optical density could be ascribed possibly to dilution by an associated hydramnios, not always apparent clinically. The false-negative results could be considered as part of the immediate scatter around the hyperbola, and all were from pregnancies of less than 38 weeks gestation.

Twenty-four samples were obtained from patients with spontaneous rupture of membranes. In these specimens, vaginal contamination probably increased the optical density at 650 nm and as a result, the number of false-positive results was increased (Table III).

DISCUSSION

Sbarra *et al* (1977) have tested amniotic fluids at both 400 nm and 650 nm. They considered that the latter wavelength was a better choice, because of possible interference by bile pigments at the shorter wavelength. Arias *et al* (1978) also tested at both wavelengths and found there was little to choose between them. We have followed Sbarra *et al* (1977) in choosing to measure optical density at 650 nm.

The data obtained from amniocentesis samples was well represented by a hyperbola. The 'false-positive' and 'false-negative' samples can be considered as part of the close scatter about such a hyperbola, and any optical density cut-off point should be well removed from the junction of the scatter with the 'L/S ratio of 2·0' line (Fig. 1).

All these samples show such low values of

TABLE II

Analysis of results on amniotic fluid obtained by amniocentesis

Type of result	Number (n = 158)	Per cent
False-positive	2	1·3
False-negative	11	7·0
Immature	28	17·7
Mature	117	74·0

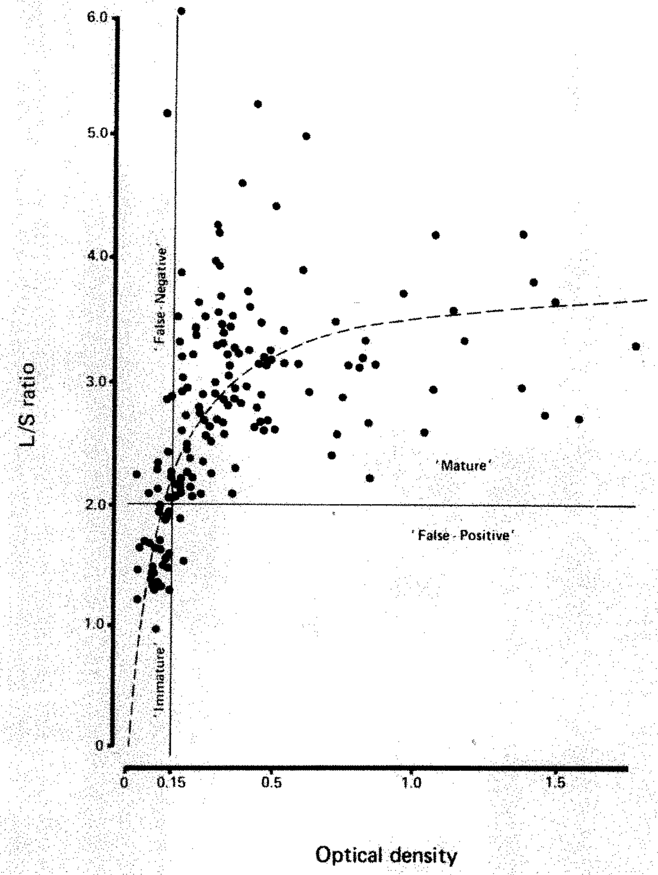

FIG. 1
L/S ratio versus optical density at 650 nm. For description of sectors see first paragraph of 'Results'.

TABLE III
Analysis of results on amniotic fluid obtained by vaginal aspiration

Type of result	Number
False-positive	5
False-negative	0
Immature	2
Mature	17

optical density that L/S ratio determinations would be required as a matter of routine, and their unusual nature would then become apparent. In contrast to optical density measurements L/S ratios are not volume-dependent.

The implications of our experience with the optical density test are that it would prove to be extremely valuable as a screening procedure for fetal pulmonary maturity and would reduce substantially the laboratory workload of L/S measurements. The optical density determination requires only five to ten minutes to perform as against some two to three hours for the L/S ratio under batch conditions. By using the appropriate cut-off point on the optical density, only values below this would require a confirmatory L/S ratio to be performed; values above this could be described as 'mature', and a ratio would not be needed.

The cut-off point of 0·10 has been proposed by Copeland *et al* (1978) and 0·15 by Sbarra *et al* (1977). In our experience the former would

TABLE IV

The effect of varying the OD 'cut-off point' on the efficiency of the method

OD cut-off point	No. of samples judged as 'immature' by OD	Per cent	No. of samples judged as 'immature' by ratio	Per cent
0·10	15	9·5	13	8·2
0·15	39	24·7	28	17·7
0·20	58	36·7	30	19·0
0·25	72	45·6	30	19·0
0·30	85	53·8	30	19·0

produce too many false-positive results while the latter (0·15) is considerably better. We consider that a value higher than 0·15 is needed, probably 0·20 or even 0·25, to remove as completely as possible the occurrence of such false-positive values. Unfortunately, the number of L/S ratio determinations required would also rise in consequence, but it is still possible to reduce the total number of determinations by up to 55 per cent (i.e. from 158 to 72) even if the higher level of 0·25 optical density were adopted. If the 0·20 cut-off be chosen, the reduction in number of L/S ratio determinations is even greater (63 per cent), i.e. from 158 to 58 (Table IV).

The effect of inclusion of samples from patients with ruptured membranes is to increase the number of false-positive results from two to seven, and the optical density values then lie beyond any reasonable cut-off point (Table III). It is therefore recommended that such types of sample be excluded from measurement by optical density, and their L/S ratios determined as a matter of course.

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THE EFFECTS OF ERGOMETRINE ON THE LOWER OESOPHAGEAL SPHINCTER TONE AT CAESAREAN SECTION

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Summary

The effect of intravenous ergometrine 0·5 mg during general anaesthesia for Caesarean section on lower oesophageal sphincter (LOS) function was investigated in eight patients. Ergometrine increased the LOS pressure markedly ($p < 0{\cdot}005$).

Regurgitation and inhalation of acid gastric contents with resultant chemical pneumonitis, remains a major cause of maternal death associated with both the induction and recovery phases of general anaesthesia (Arthure *et al*, 1969; Scott, 1978); the importance of the lower oesophageal sphincter (LOS) as a barrier to reflux of acid gastric contents into the oesophagus is well documented (Pope, 1967; Lipshutz *et al*, 1973; Brock-Utne *et al*, 1976; Hey *et al*, 1977).

Ergometrine is rountinely used in many centres after delivery although vomiting occurs in 20 per cent of cases after parenteral administration (Goodman and Gilman, 1970). No data are currently available as to the effect of ergometrine on the lower oesophageal sphincter. If ergometrine has a beneficial effect by increasing the lower oesophageal sphincter tone, this would be an advantage in view of the drug's potential for inducing vomiting. This paper therefore presents the results of an investigation into the effect of ergometrine on the LOS during general anaesthesia for Caesarean section at term.

Subjects and Methods

Eight pregnant patients at term, who gave their informed consent, were investigated.

On the operating table, the mothers were tilted laterally by means of a 15° foam rubber wedge placed beneath the left hip (Buley *et al*, 1977). Patients inhaled pure oxygen for five minutes through a non-rebreathing anaesthetic circuit. An intravenous infusion of a balanced salt solution was started, and atropine, 0·6 mg, mixed with metoclopramide, 10 mg, was injected into the infusion tubing (Brock-Utne *et al*, 1976), followed by 2·5 mg of alcuronium to avoid the increase in gastric pressure that occurs after succinyl dicholine injection (La Cour, 1970).

Anaesthesia was induced intravenously by the injection of thiopentone, 3·5 mg/kg, and succinyl dicholine, 1·75 mg/kg body mass, freshly mixed in the same syringe. The rationale behind this induction sequence has been discussed (Downing *et al*, 1974). As the patient lost consciousness, an assistant applied pressure to the cricoid cartilage and an endotracheal tube was inserted into the trachea. Ventilation of the lungs was mechanically controlled using a Manley Respirator delivering a minute volume of 120 ml/kg (Ohio Vortex Respiration Monitor). Further muscle relaxation was obtained by injecting alcuronium, 0·2 mg/kg, intravenously. Anaesthesia was maintained with 50 per cent nitrous oxide in oxygen with 0·5 to 0·8 per cent enflurane (Coleman and Downing, 1975).

Oesophageal motility studies were started once general anaesthesia was established. A motility catheter consisting of two portex polyethylene No. 54 plastic tubes fused together at their distal ends was passed through the nose until the two recording orifices, situated 5 cm and 10 cm respectively from the catheter tip, lay in the stomach. Throughout the entire procedure each tube was continuously perfused with water at the rate of 0·19 ml/minute, using a Harvard Constant Infusion Pump. Each tube was in turn connected to a Beckman Instrument Physiological Transducer (Model 215071), linked to a four channel Beckman R/511 Dynograph Amplifier and recorder.

The catheter was withdrawn slowly, 0·5 cm at a time, until the pressure reading indicated that the recording orifices had re-entered the oesophagus via the lower oesophageal sphincter (LOS), thus giving two readings of baseline gastric pressures (GP), LOS and oesophageal pressures (OP) before the intravenous injection of ergometrine. The calculated difference between LOS and GP is termed the barrier pressure (BP). With patients receiving a general anaesthetic as described above, motility recordings were performed shortly after induction of general anaesthesia (I), after the abdomen was opened (II), after the baby was born (III), after an intravenous dose of 0·5 mg ergometrine (IV), after the uterus had been returned to the peritoneal cavity (V) and shortly before the abdomen was closed (VI). Anaesthetic maintenance was identical throughout. The pressure profiles of the various phases were compared and the results analysed using a Student's t-test for two paired sample means.

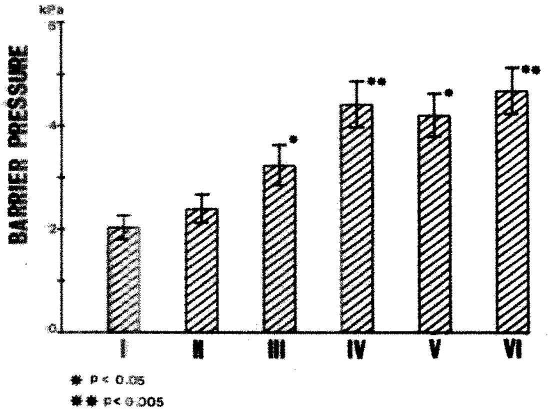

FIG. 1

Barrier pressure (kPa above atmospheric pressure) obtained at various stages during surgery. (I) Shortly after induction. (II) After abdomen was opened. (III) After the baby was born. (IV) After ergometrine. (V) After the uterus returned to the peritoneal cavity. (VI) After the abdomen was closed. Significant sphincter changes occurred from I, II, and III, to IV, V, and VI. (* $p < 0{\cdot}01$, ** $p < 0{\cdot}005$).

RESULTS

The results are shown in Tables I and II and Figure 1. Compared to the three phases, induction, laporotomy, and delivery of the baby the sphincter and barrier pressure (BP) rose after ergometrine injection in all patients studied; the mean differences were highly significant. The onset of this action was within one minute, and lasted at least 45 minutes up to the end of general anaesthesia.

DISCUSSION

The routine injection of ergometrine to produce uterine contraction after delivery of the fetus is well established. The increase in LOS tone observed here following the administration of ergometrine has not, to our knowledge, previously been reported.

Aspiration of acid gastric content into the lungs, resulting in Mendelson's syndrome (Mendelson, 1946) remains a significant cause of morbidity and mortality in obstetrics (Arthure *et al*, 1969; Scott, 1978). Ergometrine's beneficial effect on the lower oesophageal sphincter should assist in preventing passive regurgitation of stomach contents. However, ergometrine is an emetic and induced vomiting may be dangerous, especially in a patient who cannot guard her airway, for example, at the end of general anaesthesia.

TABLE I

*Individual results in eight patients**

	Pressures (kPa above atmospheric pressure)																	
	(I) Post-induction			(II) Laparotomy			(III) Birth			(IV) Ergometrine			(V) Uterus back into peritoneal cavity			(VI) Abdomen closed		
Patient No.	GP	SP	OP	GP	SP	OP	GP	SP	OP	GP	SP	OP	GP	SP	OP	GP	SP	OP
1	3·2	5·6	1·7	2·9	5·0	1·8	1·9	4·6	1·7	2·2	7·0	1·8	2·2	7·3	2·0	2·0	7·2	1·8
2	3·6	4·7	2·0	—	—	—	2·5	4·0	2·3	2·8	7·3	2·2	3·3	6·4	2·1	3·1	6·5	2·1
3	3·1	5·6	1·6	2·5	5·7	1·8	1·4	6·4	1·3	1·5	7·8	1·4	1·6	7·9	1·4	1·8	9·1	1·4
4	3·0	4·9	1·6	—	—	—	1·8	2·9	1·0	2·0	4·4	0·9	2·0	3·3	0·8	1·9	3·4	0·7
5	2·1	3·0	1·6	2·0	3·4	1·6	2·3	4·1	0·8	1·4	8·3	0·8	1·4	8·0	1·0	1·9	8·0	0·8
6	2·0	3·9	1·9	2·2	4·1	1·6	1·6	3·4	1·0	1·5	5·2	1·1	1·4	7·3	1·0	2·0	6·6	1·2
7	1·9	4·6	1·5	2·0	4·8	1·7	2·4	5·0	1·0	1·7	5·2	1·0	1·7	5·0	0·8	1·5	5·7	0·6
8	2·0	3·2	1·0	2·0	3·4	1·5	1·8	2·8	0·8	2·0	6·8	1·2	1·8	7·2	0·8	2·2	6·5	0·8

* In patients No. 2 and 4, the delivery of the infant was too quick for any values at laparotomy to be obtained.

GP = gastric pressure.

SP = sphincter pressure.

OP = oesophageal pressure.

TABLE II

Gastric, sphincter, oesophageal pressures at various stages during surgery. Note the significant increases from post-induction, laparotomy and birth to IV, V and VI in both sphincter and barrier pressures

		Pressures (kPa above atmospheric pressure)					
		(I) Post-induction	(II) Laparotomy	(III) Birth	(IV) Ergometrine	(V) Uterus back into peritoneal cavity	(VI) Abdomen closed
Gastric pressure (GP)	Mean SEM	2·58 0·19	2·50 0·17	1·87* 0·1	1·98 1·1	2·40 0·16	2·19 0·14
Sphincter pressure (SP)	Mean SEM	4·61 0·26	4·89 0·34	5·10* 0·42	6·38** 0·40	6·59** 0·43	6·85** 0·43
Oesophageal pressure (OP)	Mean SEM	1·26 0·17	1·57 0·17	1·21 0·17	1·41 0·12	1·34 0·13	1·13 0·16
Barrier pressure (BP)	Mean SEM	2·03 0·23	2·39 0·28	3·23* 0·39	4·40** 0·45	4·19* 0·42	4·66** 0·45

Significant changes in barrier pressure I to IV $p < 0{\cdot}005$ ($t = 4{\cdot}812$) I to V $p < 0{\cdot}01$ ($t = 3{\cdot}834$) and I to VI $p < 0{\cdot}005$ ($t = 4{\cdot}383$).

* $p < 0{\cdot}05$

** $p < 0{\cdot}005$

In the six phases of anaesthesia studied here, little change in intragastric and oesophageal pressures was observed. However both LOS and therefore barrier pressures were significantly increased after ergometrine, and were maintained up to the end of anaesthesia uninfluenced by the surgical manoeuvres.

The mechanism of action of ergometrine on the LOS is unknown, but Johnson (1972) has shown that the drug constricts blood vessels controlled by alpha-adrenoreceptors in man, The vasoconstrictive effect of ergometrine has a much wider distribution than that associated with sympathetic activity or sympathetic drugs alone. The widespread vasoconstriction caused by ergometrine increases the total peripheral resistance thus raising both central venous and mean arterial pressures (Brooke and Robinson, 1970). Indeed, accidental ergometrine overdose is associated with prolonged peripheral vasoconstriction which may ultimately lead to ischaemic gangrene. The ability of ergometrine to increase profoundly central venous pressure in obstetric patients is on occasions undesirable, especially where hypertension is already present (Johnson, 1972).

Our method of LOS pressure measurements during anaesthesia was virtually identical to that of Hill (1978), who tried several other methods of measuring pressures using balloons, pressure probes and air-filled tubes during anaesthesia, but found all to be unsatisfactory.

The method of studying gastro-oesophageal motility using a catheter 'pull through' technique and thereby obtaining a pressure profile has proved satisfactory to many workers (Earlam, 1975; Code and Schlegel, 1974; Hey *et al*, 1977; Pope, 1974; Haddad, 1970). An alternative technique was used by Smith *et al* (1978) who left the tube in the sphincter to obtain a continuous reading. Leaving the tube in the LOS is fraught with possible inherent faults. The LOS is a dynamic sphincter and a single lateral orifice related only to one side of the sphincter may give unrepresentative high or low values; furthermore, the tube with its lateral orifice may also slip wholly or partially out of the LOS giving falsely low readings. Our own tubes are assembled in such a way that the lateral orifice points in different directions, hence the mean of these values gives a more representative estimation of LOS pressure.

In conclusion, ergometrine consistently increased LOS tone during general anaesthesia for Caesarean section without altering gastric or oesophageal pressure significantly. Further investigation in both unanaesthetized human volunteers and the pregnant patients at term, both pre- and post- delivery would seem indicated.

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AN ANALYSIS OF THE INFLUENCES OF MATERNAL AGE, GESTATIONAL AGE, CONTRACEPTIVE METHOD, AND THE MODE OF PRIMARY TREATMENT OF PATIENTS WITH HYDATIDIFORM MOLES ON THE INCIDENCE OF SUBSEQUENT CHEMOTHERAPY

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Summary

In relation to the total number of births in the United Kingdom there was an excess of hydatidiform moles arising in women over 34 years of age and possibly also under 15. The incidence of trophoblastic tumour requiring chemotherapy after hydatidiform mole was greatest in the 30 to 34 year age group and it was also high in the 20 to 24 year age group. This distribution appears to be influenced by the morphology of the moles, the mode of their removal and the use of oestrogens and progestogens in the post-evacuation period. The need for chemotherapy for trophoblastic tumour after evacuation of a hydatidiform mole was found to be two- to three-fold greater in patients who had undergone a medical induction, hysterectomy or hysterotomy compared with those whose hydatidiform moles had been evacuated by vacuum or surgical curettage, or who had aborted spontaneously. The increased risk of chemotherapy was most marked in the earlier weeks of gestation.

THE proportion of patients who receive chemotherapy for invasive mole or choriocarcinoma developing after evacuation or removal of a hydatidiform mole has been reported as 5·6 per cent (Bagshawe *et al*, 1973), 19 per cent (Curry *et al*, 1975) or 26 per cent (Morrow *et al*, 1977).

Variability in the methods used to remove hydatidiform moles and differing criteria for using chemotherapy make it difficult to examine the relation between the method of initial treatment and the need for subsequent chemotherapy when data from different centres are compared.

We now examine the methods of evacuating or removing hydatidiform moles and the subsequent need for chemotherapy by studying the records of patients notified to the Royal College of Obstetricians and Gynaecologists (London) since 1972. We have related patient age to mode of evacuation and to the development of invasive mole or choriocarcinoma, by examining the records of the group of patients previously reported by Stone *et al* (1976). In addition, the gross morphology of the moles and the use of oestrogen/progestogen preparations in the period after evacuation of the mole have been related to outcome.

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METHODS

We analysed the records of 611 consecutive patients whose names had been given to the Register established by the Royal College of Obstetricians and Gynaecologists (London) and the Department of Health and Social Security. Hydatidiform mole was diagnosed on the basis of gross macroscopic appearance or by microscopic examination by the pathologists at the referring hospitals. All 611 patients were registered during the 30 months preceding February 28th, 1975 and within two months of initial treatment for the hydatidiform mole. All patients were followed up regularly with assays for human chorionic gonadotrophin done in our laboratory on timed urine collections. Details of the method of follow-up and the criteria for selecting patients for treatment by chemotherapy have been defined (Bagshawe *et al*, 1973; Stone *et al*, 1976) and were applied uniformly to the series.

The registration forms completed by the referring gynaecologist provided the source of information about initial treatment, duration of gestation, gross morphological classification and the patient's age. The primary modes of evacuation or removal of hydatidiform moles were: spontaneous abortion (S), which sometimes was followed by curettage or vacuum aspiration of the uterus; dilation and curettage (D); vacuum curettage (V); medical with oxytocin or prostaglandins (M); hysterotomy or hysterectomy (H); salpingectomy for ectopic pregnancy (E). In some patients, the method of primary treatment was not recorded (NR).

Of the 611 patients, 61 required chemotherapy. The treated patients had a complete history taken and their registration data confirmed. A sample of 288 patients out of the 550 who did not have chemotherapy was analysed to obtain information concerning duration of gestation.

The gross morphological classification of the moles of 30 of the 61 patients who required chemotherapy was recorded and also that for a random sample of 320 of the remaining 550 patients who did not require chemotherapy.

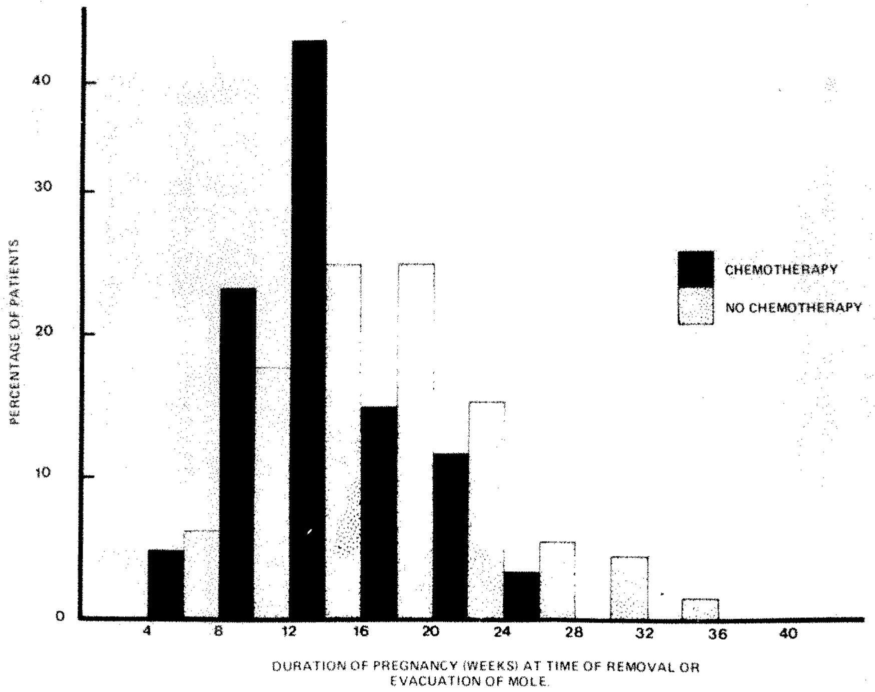

FIG. 1
Histogram showing incidence of chemotherapy according to duration of pregnancy.

TABLE I

Incidence of chemotherapy according to mode of evacuation or removal of mole

	Mode of evacuation									
	Spontaneous abortion (S)	Dilatation and curettlage (D)	Vacuum aspiration (V)	Ectopic pregnancy (E)	S+D+V+E	Medical induction (M)	Hysterotomy or hysterectomy (H)	M+H	Not recorded	Total
No chemotherapy	139	125	88	11	363	130*	24	154	33	550
Chemotherapy	9	10	4	0	23	32	6	38	0	61
	(6·1%)	(7·4%)	(4·3%)		(6·0%)	(19·8%)	(20·0%)	(19·8%)		(10·0%)

* One patient who had a digital evacuation of uterus has been included in this group since this may have followed a medical induction.

TABLE II

Significance value for differences in incidence of chemotherapy after different methods of evacuation shown in Table I

Mode of evacuation	S	D	V	M
D	NS			
V	NS	NS		
M	<0·01	<0·01	<0·01	
H	<0·05	(<0·1 >0·05)	<0·02	NS

Ninety-six patients out of this random sample of 320 and 31 of the 61 requiring chemotherapy did not have adequate information to classify the mole. This provided 254 patients for whom we knew the age and the morphological classification of the mole (classical, transitional or partial).

The statistical method used to calculate all tests of significance was χ^2.

RESULTS

The incidence of treatment by chemotherapy

TABLE III

Relation of duration of gestation to incidence of treatment by chemotherapy

	Gestational age (weeks)						
	12 or less	13 or 14	15 to 20	21 to 28	29 or more	Not recorded	Total
No chemotherapy	122	82	193	115	25	13	550
Chemotherapy	18	14	19	9	0	1	61
	(12·9%)	(14·6%)	(9·0%)	(7·3%)	(0%)		(10%)

Number of patients not requiring chemotherapy in each gestational age group has been based on an analysis of a random sample of 288 registered patients. The patients who required chemotherapy have been distributed in accordance with the reported gestational age.

TABLE IV

Mode of evacuation or removal of hydatidiform mole and duration of pregnancy in relation to subsequent incidence of treatment with chemotherapeutic agents

Mode of evacuation*		Duration of pregnancy (weeks)					
		12 or less	13 or more	P	14 or less	15 or more	P
S	No chemotherapy	40	99	NS	60	79	NS
	Chemotherapy	2	7		3	6	
D	No chemotherapy	32	93	NS	50	75	NS
	Chemotherapy	4	5		6	3	
V	No chemotherapy	21	67	NS	36	52	NS
	Chemotherapy	1	3		3	1	
M	No chemotherapy	10	120	<0·02	29	101	<0·01
	Chemotherapy	8	24		16	16	
H	No chemotherapy	3	21	NS	11	13	NS
	Chemotherapy	3	3		4	2	
Total	No chemotherapy	106	400	NS	186	320	<0·02
	Chemotherapy	18	42		32	28	

* Abbreviations used are those in Table I. NS = not significant.

following the various modes of evacuation or removal of hydatidiform moles is shown in Table I. After medical induction, hysterotomy or hysterectomy, chemotherapy was required in 19·8 per cent of patients compared with 6 per cent for the other methods ($p < 0·001$). The significance of differences between the incidence of chemotherapy for the various methods or treatments are shown in Table II.

Figure 1 relates the duration of gestation to the need for subsequent chemotherapy. It can be seen that the chemotherapy group tended to have evacuations or removal of moles at an earlier stage of gestation than patients not requiring chemotherapy.

Table III shows that the incidence of chemotherapy was highest when the duration of gestation was 13 to 14 weeks and lowest after 20 weeks ($p < 0·05$). The incidence of chemotherapy was significantly higher ($p < 0·05$) when the duration of gestation was under 15 weeks rather than 15 weeks or more.

Table IV relates the incidence of chemotherapy to mode of evacuation and duration of pregnancy of the mole. Longer gestation appears to be associated with a significantly decreased incidence of chemotherapy but only in patients initially treated by medical induction was the association significant. The relationship between the incidence of chemotherapy, mode of evacuation or removal and duration of gestation is shown in Figure 2.

When the low risk (S, D, V and E) and high risk (M and H) methods of evacuation are grouped and related to the duration of gestation (Table V) it can be seen that a medical induction, hysterotomy or hysterectomy are associated with an increased incidence of chemotherapy at all durations of gestation, particularly in the first trimester.

The incidences of chemotherapy in the group of 30 patients who had hysterotomy or hysterectomy were 30 and 15 per cent respectively.

Figure 3 shows the age distribution of the 611

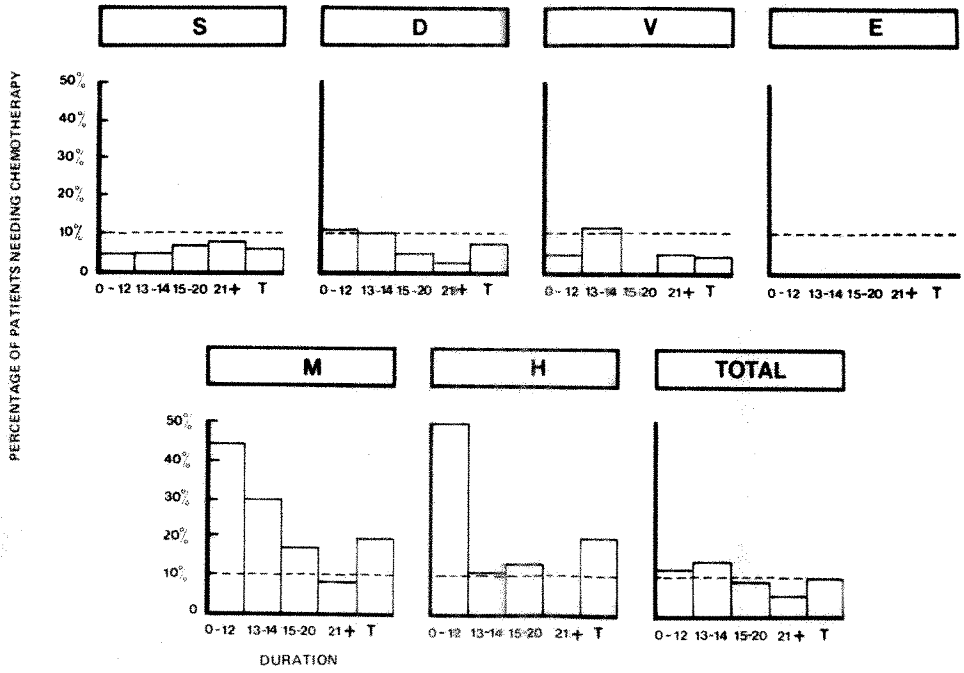

FIG. 2

Relation of mode of evacuation, duration of gestation and subsequent chemotherapy. S = spontaneous abortion; D = dilatation and curettage; V = vacuum aspiration; E = ectopic pregnancy; M = medical induction; H = hysterotomy or hysterectomy.

TABLE V

Duration of pregnancy and mode of evacuation or removal of hydatidiform mole related to incidence of chemotherapy

Duration of pregnancy (weeks)		Mode of evacuation or removal of mole				
		SDVE	MH	P	SDVE P	MH P
12 or less	No chemotherapy	104	13	<0·001	NS	<0·01
	Chemotherapy	7	11			
13 or more	No chemotherapy	259	141	<0·001		
	Chemotherapy	15	27			
14 or less	No chemotherapy	157	40	<0·001	NS	<0·01
	Chemotherapy	12	20			
15 or more	No chemotherapy	206	114	<0·01		
	Chemotherapy	10	18			
Series	No chemotherapy	363	154	<0·001		
	Chemotherapy	22	38			

* Abbreviations used are those in Table I.

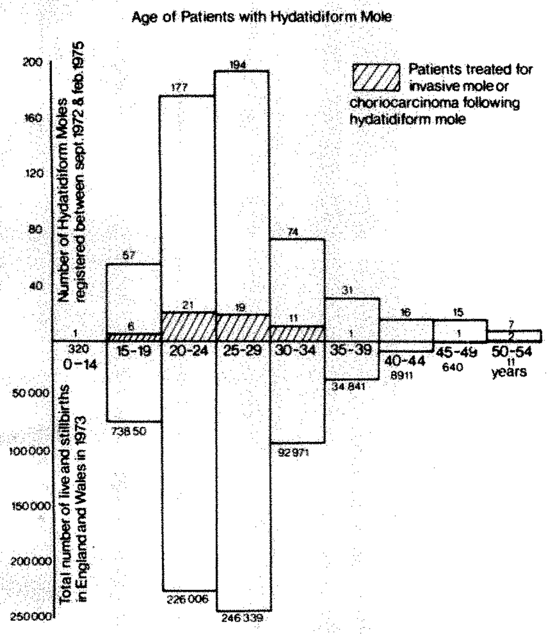

FIG. 3

Age distribution for patients with hydatidiform mole and for mothers delivered after 28 weeks gestation in England and Wales in 1973.

patients in the series, and also the age distribution of mothers delivered after 28 weeks in the United Kingdom in 1973. Between the age of 15 and 34 years, the number of hydatidiform moles registered was proportional to the total number of births. Hydatidiform moles were most frequently found in patients aged 25 to 29. This coincided with the mode of the total number of births in the United Kingdom. In patients aged over 34, there was a relative excess of hydatidiform moles compared to total births and the data suggested, but not conclusively so, an increased incidence of mole in the under 15 year age group.

Table VI has been based on the Registrar General's Statistical Review. From the data, it can be seen that there were 11 livebirths in the United Kingdom in 1973 to mothers aged 50 to 54. In the 30 months of the study, 7 hydatidiform moles were registered in this age group. The risk of hydatidiform mole complicating a pregnancy in a mother aged over 49 can be estimated to be of the order of 800 times that of a patient in the 15 to 19 year age group.

The data for patients with hydatidiform moles

TABLE VI

Total births in England and Wales for the year 1973 (Registrar General's Statistical Review) and the relation of age of patient to birth rate and incidence of hydatidiform moles

Age group (years)	Livebirths	Stillbirths	Total births	Hydatidiform moles	Hydatidiform moles per 100 000 births in 1973*
0–14	317	3	320	1	312·5
15–19	72953	897	73850	57	77·2
20–24	223 675	2331	226 006	177	78·3
25–29	243 753	2586	246 339	194	78·7
30–34	91800	1171	92971	74	80·0
35–39	34178	663	34841	31	89·0
40–44	8649	262	8911	16	179·6
45–49	617	23	640	15	2343·8
50–54	11	0	11	7	63636·4
Not recorded				39	
Total	675 953	7936	683 889	611	

* It should be noted that the hydatidiform moles were collected over the 30 months which included 1973 and includes only the cases referred to Charing Cross Hospital within two months of date of primary evacuation.

relates, of course, to those referred to Charing Cross Hospital during a 30 months period and this represents an unknown fraction (probably half) of all the hydatidiform moles occurring in England and Wales during that period.

It can be seen from Figure 3 that the age-related incidence of invasive mole or choriocarcinoma followed a different distribution from the age-related distribution of hydatidiform moles. There was a low incidence of chemotherapy between 35 to 49 (2 out of 62 patients) but a high incidence over the age of 50 (2 out of 7 patients).

Table VII shows the need for chemotherapy according to maternal age and according to the use of oestrogen/progestogen oral contraceptives after removal or evacuation of the hydatidiform mole. It can be seen that the high incidence of chemotherapy in those over 49 years of age was not related to oestrogen/progestogen usage.

Figure 4 shows the age distribution of oestrogen/progestogen users and non-users in the post-mole period and indicates the age-associated incidence of hydatidiform mole and invasive mole or choriocarcinoma in both groups. It can be seen that there was an excess of patients receiving chemotherapy amongst oestrogen/progestogen users. The 20 to 24 year age group received oestrogen/progestogen preparations in the post-mole period most frequently.

From Table VIII it can be seen that the proportion of non-classical moles appears to decrease after age 40, but the numbers of cases are too small to be conclusive.

The various modes of evacuation or removal have been related to age in Table IX. It is apparent that more patients undergo hysterectomy as primary treatment in the older age groups. Table IX also relates the observed and expected distribution of both the simple modes of uterine evacuation and of medical inductions, in the various age groups. The expected distribution was based on a uniform distribution with age of the various modes of evacuation (or removal) of hydatidiform mole. There were disporportionately fewer patients ($p < 0{\cdot}01$) receiving a medical induction at 35 or more years than under 35 years.

DISCUSSION

The main limitation of the data is the absence of information on uterine size and it is possible that uterine size influenced the method of primary treatment of the hydatidiform mole. Since most gynaecologists in the United Kingdom take 12 or 14 weeks uterine size as their normal limit for vaginal termination of preg-

TABLE VII

Association of age, oestrogen and progestogen (O/P) and ensuing tumour

Age (years)	Osetrogen/progestogen contraceptive			No contraceptives			Contraceptive technique not recorded			Percentage treated			Total and (percentage treated)
	Chemo-therapy	No chemo-therapy	Total	Chemo-therapy	No chemo-therapy	Total	Chemo-therapy	No chemo-therapy	Total	O/P	No O/P	Not recorded	
0–14	0	0	0	0	1	1	0	0	0	0	0	0	1 (0)
15–19	2	5	7	4	38	42	0	8	8	28·6	9·5	0	57 (10·5)
20–24	9	22	31	11	123	134	1	11	12	29·0	8·2	8·3	177 (11·9)
25–29	4	14	18	14	150	164	1	11	12	22·2	8·5	8·3	194 (9·8)
30–34	1	4	5	10	53	63	0	6	6	20·0	15·9	0	74 (14·9)
35–39	0	2	2	1	22	23	0	6	6	0	4·3	0	31 (3·2)
40–44	0	1	1	0	14	14	0	1	1	0	0	0	16 (0)
45–49	0	0	0	1	11	12	0	3	3	0	8·3	0	15 (6·7)
50–54	0	0	0	2	4	6	0	1	1	0	33·3	0	7 (28·6)
Not recorded	0	1	1	0	31	31	0	7	7	0	0	0	39 (0)
Total	16	49	65	43	447	490	2	54	56	24·6	8·8	3·6	611 (10·0)

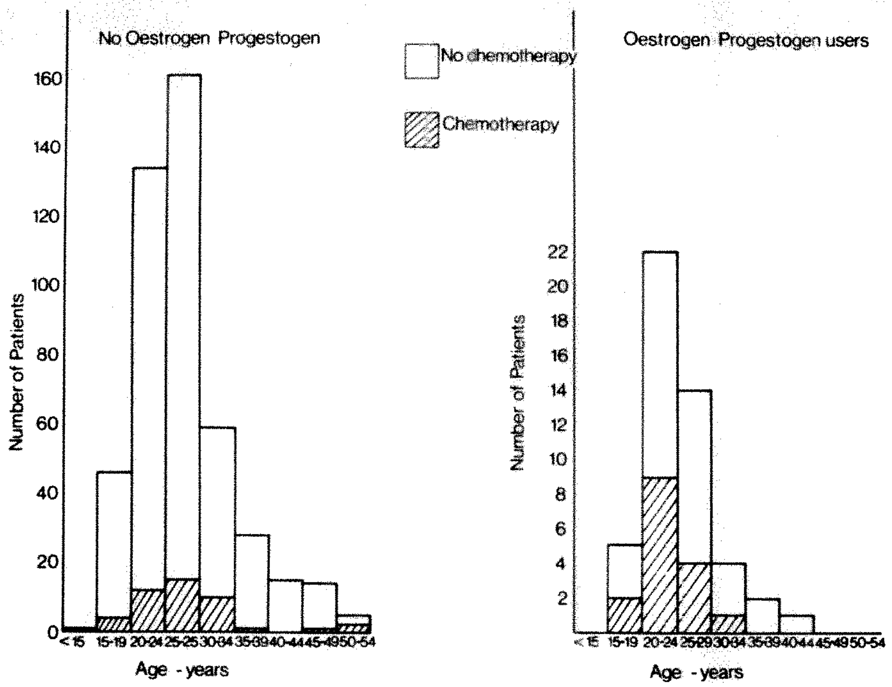

FIG. 4

Age distribution of patients who did, or did not, receive oestrogen/progestogen contraceptives. The 56 patients about whom there was inadequate information about contraceptive technique were included in the 'no oestrogen progestogen' group.

TABLE VIII

Relation of morphology of hydatidiform mole to maternal age

	Type of hydatidiform mole			
Age (years)	Classical	Non-classical	Total	Percentage non-classical
0–14				
15–19	17	7	24	29·2
20–24	52	15	67	24·4
25–29	58	27	85	31·8
30–34	29	14	43	32·6
35–39	6	3	9	33·3
40–44	6	2	8	25
45–49	5		5	0
50–54	4	1	5	20
Not recorded	5	3	8	37·5
Total	182	72	254	28·3

nancy, our data might suggest that the prognosis is worse the greater the bulk of the uterus. Curry *et al* (1975) and Morrow *et al* (1977) have indicated that the risk of persistent trophoblastic disease was greatest in the patients who were large for dates.

Loudon (1959) introduced high dose oxytocin to stimulate the abortion of molar pregnancies. But Braga and Chun (1969) felt that oxytocin might precipitate trophoblast embolisation and Attwood and Park (1961) noted that the main cause of trophoblastic displacement appeared to be uterine contraction and 'placental commotion'.

The high incidence of invasive mole or choriocarcinoma after hysterectomy suggested by the data may be an artefact. One of the patients requiring chemotherapy was known to have had a hysterectomy for uncontrollable haemorrhage at the time of attempted hysterotomy for bleeding after a failed medical induction. The number of patients was small and if this patient

TABLE IX

Association of mode of evacuation and incidence of chemotherapy in relation to the age of the patient

Mode of evacuation	Age of patient (years)										Total
	0–14	15–19	20–24	25–29	30–34	35–39	40–44	45–49	50–54	Not recorded	
SDVE†											
Observed	1	38(2)	112(10)	128(6)	48(3)	17	12	6	4(2)	20	386(23)
Expected		36	111·8	122·6	46·7	19·6	10·1	9·5	4·4	24·6	
Medical											
Observed		16(3)	52(9)	57(12)	23(8)	5	1	1	0	7	162(32)
Expected		15·1	46·9	51·4	19·6	8·2	4·2	4·0	1·9	10·3	
Hysterotomy											
Observed		1(1)	2(1)	2(1)	0	1	0	1	0	3	10(3)
Expected		0·9	2·9	3·2	1·2	0·5	0·3	0·2	0·1	0·6	
Hysterectomy											
Observed		0	2(1)*	0	2	3(1)	2	7(1)	3	1	20(3)
Expected		1·9	5·8	6·4	2·4	1·0	0·5	0·5	0·2	1·3	
Not recorded											
Observed		2	9	7	1	5	1	0	0	8	33
Expected		3·1	9·6	10·5	4·0	1·7	0·9	0·8	0·4	2·1	
Total	1	57(6)	177(21)	194(19)	74(11)	31(1)	16	15(1)	7(2)	39	611(61)

Figures in parenthesis are number of patients receiving chemotherapy.

* This patient had a hysterotomy performed for a failed medical induction due to haemorrhage. Hysterectomy was eventually required to control bleeding.

† For abbreviations see Table I.

had been classified as a hysterotomy, the risk of hysterotomy would have been 36·4 per cent and that of hysterectomy 10·5 per cent. Early clamping of the uterine veins and the decreased risk of spillage of cells at hysterectomy may account for the lower risk compared with hysterotomy.

Since Brandes *et al* (1966) described the vacuum aspiration of molar tissue irrespective of uterine size, its proponents have claimed that negative pressure limits dissemination of trophoblast, is rapid and reduces the blood loss to a minimum. The present analysis appears to confirm the superiority of vacuum aspiration and the low risk of a subsequent need for chemotherapy. But trophoblast embolisation is likely to be increased if ergometrine is given at the time of vacuum aspiration and this drug should be avoided if possible.

Our data show that the risk of a hydatidiform mole increased as maternal age advances beyond 40 years and that there might also be an excess of patients in the very young. Similar findings have been reported by Douglas (1959), Edmonds (1959), Wei and Ouyand (1963), Chun *et al* (1964), Slocumb and Lund (1969) although Marquez-Monter *et al* (1963) did not find advanced age an aetiological factor, but they only analysed 104 patients.

Our information about gross morphological appearances was incomplete but the available data suggested complete moles are relatively more common than partial moles in the older age groups. We (Stone and Bagshawe, 1976) pointed out earlier that classical hydatidiform moles carried a higher risk than partial moles. The precise risk of a trophoblastic tumour after a partial mole will require further detailed study.

The relatively low incidence of chemotherapy for invasive mole or choriocarcinoma in the older woman is unlikely to be due to the small number of patients for analysis. Bagshawe (1969) reviewed 802 cases of choriocarcinoma in the literature and concluded that the UK and USA data suggested that the mode was in the 21 to 30 age group (as in the present series) in contrast to the Asian series where the mode was in the 31 to 40 year age group.

Medical inductions were used infrequently for women over 35 years of age. This seems likely to have contributed to the lower incidence of trophoblastic tumour in the older woman. Conversely, the more frequent use of this mode of evacuation in women of 30 to 34 years of age may have contributed to the high incidence of trophoblastic tumours in this age group.

Stone *et al* (1976) established an increased incidence of chemotherapy in patients receiving oestrogen and progestogen preparations after primary treatment of a mole. The less frequent use of these preparations in the older patients may also have contributed to the low incidence of trophoblastic tumour in these patients. Hydatidiform moles were most frequent amongst women aged 25 to 29, but invasive mole and choriocarcinoma was most frequent in women aged 20 to 24 years. The latter age group used oestrogen/progestogen preparations more frequently than others.

In this series hysterectomy was most frequently used in the older patient. Its use in this age group was probably associated with a low incidence of invasive mole and choriocarcinoma. In women of mature years, who have completed their family, hysterectomy as a primary mode of treatment would apparently not be contraindicated.

The relation between gravidity and hydatidiform moles has not been analysed in the present study. Bagshawe (1969) reported that the ratio of first to subsequent pregnancies was 1:1·38 for patients with histologically confirmed choriocarcinoma and for all patients treated for trophoblastic disease it was 1:0·95. He pointed out that in the UK and USA, the risk of choriocarcinoma appeared to be greater with first pregnancies than with subsequent pregnancies. An increased risk in first pregnancies would contribute to the increased incidence of chemotherapy noted in our younger patients.

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CHLORMETHIAZOLE TREATMENT AND BREAST FEEDING

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Summary

Four mothers receiving chlormethiazole for pre-eclampsia and their babies were the subjects of the investigation. Blood samples at delivery and blood and breast milk samples in the postpartum period were analysed for chlormethiazole. Concentrations ranged from 1·340 to 1·640 μg/g of sample in umbilical artery blood at birth, and fell to 0·010 to 0·153 μg/g in capillary blood 20 to 26 hours later. After the start of breast feeding, chlormethiazole in the babies was detectable in only 3 out of 27 serial blood samples and was 0·018, 0·009 and 0·006 μg/g. The highest calculated amount of chlormethiazole ingested at a breast feed was 37·2 μg. It is suggested that breast feeding should not be delayed solely on account of chlormethiazole therapy.

THIS investigation was undertaken to determine whether maternal treatment with chlormethiazole should influence the management of breast feeding.

Since the introduction of chlormethiazole edisylate (Heminevrin, Astra Chemicals Ltd) for the treatment of eclampsia and pre-eclampsia in the Aberdeen Maternity Hospital in 1966 it has remained a treatment of choice; the regimen has been described by Duffus *et al* (1969). The optimum therapeutic level is achieved when there is drowsiness such that sleep readily occurs in the absence of disturbance but ready awakening and intelligent communication remains possible.

Chlormethiazole is administered intravenously during labour or when eclampsia threatens; otherwise it is given orally, 1 g every six to eight hours. After delivery, intravenous therapy is stopped when urine output is satisfactory and treatment by mouth is continued until proteinuria disappears and the blood pressure starts to decline or remain stable.

The mother with proteinuric pre-eclampsia who wishes to breast feed usually has the baby put to the breast on the second day. If the mother or the baby is not well enough for breast feeding the breasts are stimulated by manual expression of milk. The establishment of breast feeding is likely to take longer in mothers who have had pre-eclampsia; therefore it is important that putting the baby to the breast should not be delayed unnecessarily.

In answering the question as to whether breast feeding should be delayed on account of chlormethiazole therapy it is necessary to have some knowledge of the following: the blood levels in the baby at birth, the elimination of the drug by

TABLE I

Clinical information about the four mothers and babies in the study

	Patient No.			
	1	2	3	4
Age (years)	26	22	20	25
Maternal weight (kg)	80	53	74	77
Gestation (weeks)	36	39	41	38
Type of pre-eclampsia*	Moderate	Moderate	Severe	Mild, complicating essential hypertension
Analgesia	Epidural	Spinal	Epidural and pudendal nerve block	Epidural
Mode of delivery	Kielland's forceps	Caesarean section	Kielland's forceps	Haig-Ferguson forceps
Birth weight of baby (kg)	3·3	2·4	3·7	3·0
Apgar minus colour score at 1, 5 and 10 minutes	8, 8	4, 5 and 8	5, 8	6, 7 and 8
First attempt at breast feeding (hours after birth)	48·5	117·7	29·3	23·0

* Pre-eclampsia was defined as moderate if the urine contained 0·25 to 2·0 g of protein/l (Esbach), and mild or severe if the proteinuria was below or above these limits.

TABLE II

Chlormethiazole edisylate (Heminevrin) dosage in the four mothers with pre-eclampsia

	Patient No.			
	1	2	3	4
Dose of oral chlormethiazole given antepartum (g)	1·0*	1·0	Nil	1·0
Interval between doses (hours)	6	6		8
Duration of treatment (days)	12	3		6
Total chlormethiazole given IV during labour (g)	2·96	2·40	4·76	5·54
Mean dose rate (mg/minute)	6·5	4·3	5·4	9·1
Duration of labour (hours)	7·6	9·3	14·7	10·2
Total chlormethiazole given IV postpartum (g)	0·88	0·80	1·64	1·26
Mean dose rate (mg/minute)	6·7	1·6	3·0	2·9
Duration of treatment (hours)	2·2	8·2	9·1	7·2
Dose of oral chlormethiazole given postpartum (g)	1·0	1·0	1·0	1·0
Interval between doses (hours)	6	6**	6**	8
Duration of treatment (days)	4	5	4	3

IV = Intravenously (as the 0·8 per cent solution).

Chlormethiazole treatment by mouth was continuous up to the induction or onset of labour, and was recommenced eight hours after delivery (day 0).

* Dosage reduced to 0·5 g from day 8 to day 2.

** Dosage interval reduced to 8 hours from day 3.

the baby and the quantities the baby will ingest as a result of breast feeding.

PATIENTS

Informed written consent was obtained from four mothers for the taking of blood and breast milk samples from themselves and blood samples by heel-prick from their babies. It was made clear that they could withdraw themselves or their babies from the investigation at any time.

The relevant clinical details of the four patients are given in Table I. Details of chlormethiazole edisylate administration are given in Table II. The rate of intravenous dosage in all four patients was determined by the response, as outlined in the introduction. All four mothers remained able to communicate throughout labour and delivery.

TABLE III

Blood concentrations of chlormethiazole at delivery in the mother, umbilical artery and umbilical vein

	Chlormethiazole concentration in blood (μg/g)			
Patient No.	Maternal vein (MV)	Umbilical artery (UA)	Umbilical vein (UV)	UA:MV ratio
1	1·79	1·53	1·26	0·85
2	1·34	1·44	1·25	1·07
3	1·59	1·34	1·30	0·84
4	2·14	1·63	1·39	0·76

TABLE IV

Chlormethiazole levels in maternal vein blood and breast milk after cessation of therapy and infant blood after delivery. Times of sampling are written in parentheses as the interval in hours following the last dose of chlormethiazole or for infant blood hours after delivery

	Chlormethiazole levels (μg/g of sample)		
Patient No.	Maternal vein blood	Breast milk	Infant blood*
1	0·12 (12) 0·03 (28)	0·21 (4) 0·21 (5) 0·08 (12) 0·01 (28)	1·530 (0) 0·094 (26) 0·000 (48)
2	0·50 (4) 0·31 (6) 0·09 (14) 0·01 (28)	0·38 (4) 0·20 (6) 0·07 (14) 0·02 (12)	1·440 (0) 0·010 (25) 0·000 (67) 0·000 (100)
3	0·63 (5) 0·27 (8) 0·24 (12) 0·13 (16) 0·05 (28)	0·67 (5) 0·35 (8) 0·31 (12) 0·15 (16) 0·04 (28)	1·340 (0) 0·093 (26) 0·054 (28) 0·000 (46)
4	0·41 (5) 0·19 (8) 0·13 (12) 0·10 (16) 0·05 (28)	0·28 (5) 0·18 (8) 0·11 (16) 0·04 (28)	1·640 (0) 0·239 (18) 0·153 (20) 0·018 (39) 0·009 (41) 0·000 (66)

* The first result is from umbilical artery and subsequent ones are from heel prick blood.

TABLE V

Chlormethiazole levels after the first breast feed. The number of samples analysed is in parentheses

	Patient No.			
	1	2	3	4
Total dose of chlormethiazole given to mother in 48 hours after first breast feed (g)	8	0	8	6
Highest maternal blood level of chlormethiazole (μg/g)	1·39 (9)	0·31 (3)	1·64 (14)	1·72 (15)
Highest level of chlormethiazole in breast milk (μg/g)	0·63 (11)	0·20 (3)	3·23 (15)	1·10 (14)
Highest level of chlormethiazole in infant blood (μg/g)	0·000 (7)	0·000 (4)	0·006 (8)	0·018 (8)
Age of infant at first breast feed (hours)	48·5	117·7	29·3	26·0

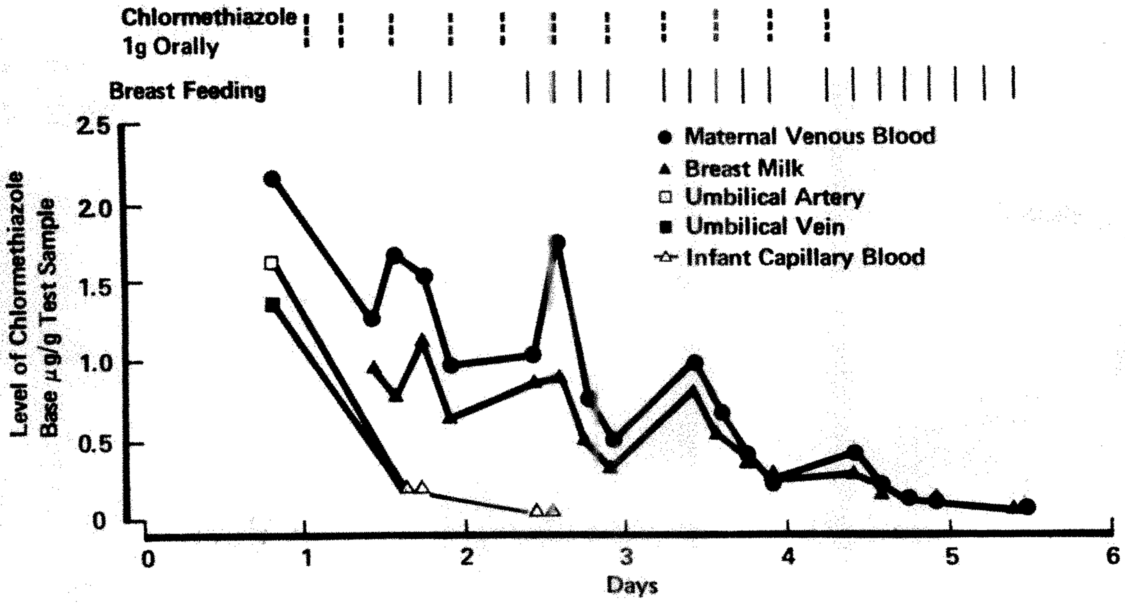

FIG. 1

Blood and milk levels of chlormethiazole and the timing of breast feeding and chlormethiazole therapy in patient No. 4.

Concomitant medication was as follows: oxytocin 5 to 10 units was administered by injection at delivery in all patients. Patients No. 3 and 4 had oxytocin infusions during labour. All patients received 15 ml of magnesium trisilicate mixture BPC orally two-hourly during labour. Patient No. 2 received methadone 7·5 mg intramuscularly at two and nine hours after delivery. Patient No. 3 received pethidine 100 mg intramuscularly at 10 and 5 hours before delivery. Patient No. 4 received promazine 25 mg intramuscularly at 72 hours after delivery. Two tablets of dextropropoxyphene 32·5 mg combined with paracetamol 325 mg (Distalgesic) were taken after delivery by patient No. 1 at 26 and 36 hours; by patient No. 3 at 25, 29, 49, 53, 65, 73, 81 and 95 hours; and by patient No. 4 at 20, 44 and 68 hours.

METHOD

At delivery the cord was double-clamped and umbilical artery, umbilical vein and maternal vein blood samples taken. From the following day breast milk samples were obtained by manual expression at approximately one or more of the following times: 0600, 1000, 1400, 1800 and 2200 hours. Maternal vein samples were timed to coincide with milk samples. Baby blood samples (0·5 g) were obtained by heel-prick twice daily. Once breast feeding had started the first sample was taken just before a feed and the next about two hours later and babies were test weighed. All samples were stored at −20 °C. The analysis of chlormethiazole in milk and blood was achieved by a direct application of a previously described mass fragmentographic method (Jostell *et al*, 1978) with a lower detection limit of 1 ng chlormethiazole/g of sample. Chlormethiazole edisylate 1 g is equivalent to 0·63 g chlormethiazole (base).

RESULTS

The concentrations of chlormethiazole in maternal and cord blood at delivery are shown in Table III.

The decline in chlormethiazole levels in maternal blood and milk following cessation of chlormethiazole therapy and in the infant after delivery is shown in Table IV.

Table V shows maximum chlormethiazole levels in all samples from the baby in the period after the first breast feed. In patients No. 1 and 2 there were no detectable levels of chlormethiazole in any infant heel-prick samples. It was detectable only once in patient No. 3 at 0·006 μg/g of blood and twice in patient No. 4 at 0·018 and 0·009 μg/g of heel-prick blood.

Table VI shows the amounts of chlormethiazole ingested by the baby at breast feeds. All four babies were fully breast feeding when discharged from hospital.

Figure 1 illustrates the details of patient No. 4. It can be seen that breast milk levels followed blood levels. The other patients showed a similar pattern.

TABLE VI

Calculated amounts of chlormethiazole ingested by the baby

Patient No.	Age of infant (hours)	Amount of milk ingested* (g)	Amount of chlormethiazole in the ingested milk (μg)
1	52	10	6·3
	60	30	6·9
	71	30	8·1
	76	20	4·0
	80	10	2·5
	83	40	14·8
	95	70	14·7
	103	60	4·8
2	118	40	8·0
	126	40	2·8
	140	50	1·0
3	29	20	33·6
	33	10	32·3
	49	10	18·0
	69	30	37·2
	73	30	18·3
	77	20	20·2
	81	20	8·6
	93	50	33·5
	97	90	31·5
	101	80	24·3
	105	70	10·5
	117	70	2·8
4	26	10	6·3
	38	10	8·6
	46	10	4·9
	50	20	6·2
	62	45	35·6
	66	50	26·5
	70	40	14·8
	74	20	4·4
	86	70	19·6
	90	50	9·0
	98	55	6·1
	110	100	4·0

* As estimated by test weighing.

DISCUSSION

Chlormethiazole is a sedative and potent anticonvulsant, which crosses the placental barrier to the baby (Duffus *et al*, 1968). If the baby is sufficiently affected it is sleepy and slow to feed, and there is hypotonia and an impaired metabolic response to cold stress (Cree *et al*, 1973). In the 12 year experience of this hospital, these problems have been found to be readily surmountable. The preterm babies are protected by modern methods of care; term babies who are otherwise well need no special attention.

This investigation was concerned with mothers and babies who were well enough to succeed at breast feeding but needed to continue with sedation with chlormethiazole for several days post partum. The side effects in the newborn infant from psychotropic agents excreted through breast feeding have been reviewed (Ananth, 1978). Caution was advised with regard to barbiturates and the author recommended the avoidance of breast feeding when the mother was receiving diazepam. Chlormethiazole was not discussed. In Aberdeen practice, chlormethiazole is usually continued for less than a week after delivery. We have shown that the amount of chlormethiazole in breast milk taken by the baby is relatively small. Compared to the dose it has received before birth the amount it gets from breast milk is insignificant. There is no evidence to suggest that low levels of chlormethiazole are harmful to the baby and we conclude that treatment of the mother for a few days post partum with chlormethiazole is no contraindication to early breast feeding. At the dose levels we used, breast feeding may begin within 24 to 48 hours of delivery.

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THE PRACTICAL VALUE OF THE PROGESTOGEN CHALLENGE TEST, SERUM OESTRADIOL ESTIMATION OR CLINICAL EXAMINATION IN ASSESSMENT OF THE OESTROGEN STATE AND RESPONSE TO CLOMIPHENE IN AMENORRHOEA

BY

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Summary

In 246 women with amenorrhoea we compared the result of the progestogen challenge test (menstrual response to oral medroxyprogesterone acetate 5 mg daily for 5 days) (225 patients) with the serum oestradiol–17β (E_2) concentration (154 patients) and with clinical assessment of the oestrogen state of the lower genital tract (183 patients) and related them to the response to clomiphene (188 patients). Ovulation in response to clomiphene was defined essentially by a mid-luteal serum progesterone concentration of at least 25 nmol/l. E_2 values were only useful when they fell below 150 pmol/l; they then indicated that ovulation was very unlikely to occur after clomiphene (2 per cent). Clinical assessment was also only useful in predicting failure to ovulate with clomiphene. However, the progestogen challenge test gave good prediction of ovulatory as well as anovulatory responses to clomiphene. After absent or scanty bleeding following progestogen, only 4 per cent of our patients ovulated, and repeated treatment with clomiphene did not increase the ovulatory rate. After a normal menstrual response to progestogen, 39 per cent ovulated in their first cycle with clomiphene using only 50 mg daily, this proportion rising to 55 per cent if 100 mg was used, and to 75 per cent after treatment for three cycles.

THE assessment of the oestrogen state is generally regarded as a useful part of the investigation of amenorrhoeic disorders (Nillius, 1979), although its place has never been clearly defined. Responsiveness to clomiphene correlates with oestrogen levels in urine and blood (Van Look, 1979) but the predictive value of quantitative oestrogen determinations has not yet been established. The variations in oestrogen levels make interpretation difficult and make biological testing attractive. The effect of administered progestogen on the endometrium, in terms of withdrawal bleeding, has been used for many years (Southam, 1965; Goldenberg *et al*, 1973; Kletzky *et al*, 1975; Nakano *et al*, 1977; Lunenfeld and Insler, 1978) and could simplify the diagnosis of amenorrhoeic disorders (Jacobs *et al*, 1975; Hull *et al*, 1976). We therefore set out to determine whether it could be used to distinguish between different causes of amenorrhoea, and also its predictiveness of the individual patient's response to clomiphene using a strict criterion of ovulation. We also compared this test ('the progestogen challenge test') with determination of serum oestradiol-17β (E_2) concentration and clinical examination of the lower genital tract.

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METHODS

Secondary amenorrhoea was diagnosed if the time elapsed since the last menstrual period was 6 months or more. Primary amenorrhoea was diagnosed by absence of menstruation at the age of 16 years or later.

We studied 249 consecutive patients with amenorrhoea but excluded two with Asherman's syndrome and one with testicular feminization, leaving 246 patients in the series; 23 patients aged 16 to 41 years had primary amenorrhoea, and 223, aged 15 to 39 years, had secondary amenorrhoea.

The causes of amenorrhoea and the diagnostic criteria used are shown in Table I. These have been outlined elsewhere (Jacobs *et al*, 1975; Hull *et al*, 1976) but were subsequently modified in that hypothalamic amenorrhoea has been subclassified (Table I) according to changes in body weight and psychological status (Hull *et al*, 1979).

In all patients a careful history was taken, with emphasis on psychological features, weight fluctuations, prolactinergic drug usage and symptoms of thyroid disorder, and a general and pelvic examination was performed. A blood sample was taken for measurement of serum follicle stimulating hormone (FSH) (reference preparation MRC 68/39) and prolactin (VLS No. 1) concentrations, using previously described radioimmunoassays (Franks *et al*, 1975), and a lateral skull X-ray was obtained. Other investigations were performed if specially indicated by these findings (Franks *et al*, 1977; Hull *et al*, 1979).

Investigations of oestrogen state and response to clomiphene

Oestrogen state was assessed by serum oestradiol-17β (E_2) concentration determination in 154 patients, by clinical assessment of the lower genital tract in 183 patients, and by the progestogen challenge test in 225 patients. In

TABLE I

The classification, distribution and diagnostic criteria of amenorrhoeic disorders in 246 patients

Diagnosis	Number of patients	Diagnostic criteria
Discrete disorders		
1° hypothalamic failure	3	Impaired FSH and LH response to LHRH (with hyposmia in hypothalamic failure)
1° pituitary failure	1	
1° ovarian failure	29	Serum FSH > 170 μg/l or 40 u/l (MRC 68/39)
Hyperprolactinaemia (pituitary tumours in 32)	60	Serum prolactin > 16 μg/l (VLS No. 1)
Polycystic ovary (PCO) disease	12	Typical ovaries with or without hirsutism or obesity
1° hypothyroidism	2	Free thyroxine index < 70 units
Hypothalamic disorders		Exclusion of all the above; subclassified by clinical features shown in first column
Chronic anorexia nervosa	30	
Other weight loss, usually stress-related	34	
Other psychological disorder, without weight loss	30	
Normal psychological state and weight	45	

addition, 188 patients were immediately treated with clomiphene according to the protocol described below. Thirteen others who were treated with clomiphene and who failed to respond had received an inadequate dose (50 mg daily). The remainder (45 patients) were not treated with clomiphene.

Serum E_2 was determined by radioimmunoassay in duplicate using a modification of the method by Hotchkiss *et al* (1971) employing a goat antiserum to E_2-6-oxocarboxymethyl oxime-BSA. Results were corrected for recovery which was monitored by an internal standard. Using 0·5 ml serum, the detection limit of the assay was 37 pmol/l (10 ng/l).

Clinical assessment was based on the appearance of the cervix and vagina and the size of the uterus. If patients had a small bright pink cervix, a bright pink vagina containing only a little serous exudate, and a small uterus, they were classified as oestrogen-deficient. Otherwise they were classed as oestrogenized or of equivocal oestrogen state; the latter was commonly due to changes associated with parity.

The progestogen challenge test consisted of assessment of vaginal bleeding in the week after oral administration of medroxyprogesterone acetate (Provera, Upjohn), 5 mg daily for 5 days. The result was classified as (1) positive, if there had been normal menstrual bleeding, (2) impaired, if there was only scanty bleeding lasting 2 days or less, or (3) negative, if no vaginal bleeding occurred. Patients were told to take 50 mg of clomiphene per day after what they judged was a positive response to progestogen, and 100 mg otherwise.

Clomiphene was given for 5 days starting one week after completing progestogen administration. In the absence of pregnancy, ovulation was diagnosed if the serum progesterone concentration was at least 25 nmol/l (8 μg/l) (determined by specific radioimmunoassay) at 12 days after completing the clomiphene administration and if menstruation occurred 5 to 10 days after the blood sample was obtained; or occasionally if the serum progesterone level was only 20 to 24 nmol/l but menstruation occurred more than 10 days later and the associated rise in basal body temperature lasted for at least 12 days. The response to clomiphene was thus classified as (1) positive if ovulation occurred, (2) impaired if menstruation occurred without an adequate rise in serum progesterone or (3) negative if there was no rise in serum progesterone and no menstruation. A response was only considered negative or impaired if a 100 mg daily dose of clomiphene had been used. There were 13 patients who had a negative or impaired response to clomiphene but never reached a 100 mg daily dose; they have been excluded from this aspect of the study.

Serum E_2 values, which were not normally distributed, were compared non-parametrically with the results of the other investigations by the Kruskal-Wallis one-way analysis of variance and the Mann-Whitney U test (two tailed). The results of the other investigations were compared by the exact chi-squared test.

RESULTS

The results of all investigations in each diagnostic class are given in Table II. The hypogonadotrophism and hypothyroidism groups were too small for useful analysis; serum E_2 levels in the former group were, however, predictably low.

Serum E_2 levels in patients with hyperprolactinaemia were significantly lower than in all other groups combined ($p < 0{\cdot}01$), and with polycystic ovarian disease they were higher ($p < 0{\cdot}05$). In patients with hypothalamic disorders, median E_2 values were significantly lower in anorexia nervosa than in those with a normal psychological state and normal weight ($p < 0{\cdot}05$).

Clinical evidence of oestrogen deficiency was common in hypogonadotrophism, primary ovarian failure and hyperprolactinaemia. It also tended to occur in anorexia nervosa, but was uncommon in patients with polycystic ovarian disease or hypothalamic disorders without psychological or body weight disturbances. Patients with primary ovarian failure, hyperprolactinaemia and hypothalamic disorders associated with psychological disturbance and weight loss usually had negative responses to progestogen challenge and clomiphene. Others tended to have positive responses.

Overall comparisons between the results of the various indices of oestrogen state are shown in Figures 1 to 3. Figure 1 shows that serum E_2 levels varied significantly with the clinical

TABLE II

Results of investigations of oestrogen state and responses to clomiphene in 246 amenorrhoeic patients

Diagnosis	Total No. of patients	Serum E_2 (pmol/l)			Oestrogen appearance‡			Response to progestogen§			Response to clomiphene§		
		Median	Range	No.	−	±	+	−	±	+	−	±	+
Discrete disorders													
Hypogonadotrophism†	4	51	37, 66	2	** 4	0	0	* 3	0	0	2	0	0
1° ovarian failure	29	106	37–356	18	***17	5	3	***21	2	3	***21	1	0
Hyperprolactinaemia	60	158	51–323	39	***21	13	5	***40	6	3	***27	11	1
PCO disease	12	316	158–374	6	1	0	9***	1	1	9***	2	2	4
1° hypothyroidism	2	—	1072	1	0	0	1	1	0	1	1	0	0
Hypothalamic disorders													
Chronic anorexia nervosa	30	176	37–499	23	*13	4	6	***23	2	3	***17	7	2
Other weight loss	34	184	99–415	13	12	10	7	***25	3	4	***15	8	2
Other psychological disorder	30	228	37–947	28	5	7	9	***19	6	5	***14	10	0
Normal psychology and weight	45	213	88–437	24	1	9	21***	9	0	35***	8	7	26***

† Hypogonadotrophism implies primary hypothalamic or pituitary failure (Table I).

‡ (−) deficient, (±) uncertain, (+) oestrogenized.

§ (−) negative, (±) impaired, (+) positive.

Significant differences between the categories of result in each test (except serum E_2) for individual diagnostic classes are indicated by asterisks (* = $p < 0{\cdot}05$, ** = $p < 0{\cdot}02$, *** = $p < 0{\cdot}01$), which are also placed to emphasize the direction of the bias. E_2 = oestradiol–17β. 1 pmol E_2 = 0·272 ng.

appearance of oestrogen state (analysis of variance: $p = 0{\cdot}005$). Serum E_2 levels in patients with obvious signs of oestrogen deficiency were lower than in those who were well oestrogenized (U test: $p = 0{\cdot}003$) or of equivocal oestrogenization ($p = 0{\cdot}013$). There was, however, no significant difference in serum E_2 levels between the last two groups. Figure 2 shows that serum E_2 levels varied significantly with the response to progestogen ($p = 0{\cdot}0001$); the levels were higher with a positive response to progestogen challenge than with either a negative ($p < 0{\cdot}0001$) or an impaired response ($p = 0{\cdot}018$), but there was no significant difference in serum E_2 levels between the last two groups. Figure 3 shows that serum E_2 levels also varied significantly with the response to clomiphene ($p = 0{\cdot}002$); the levels were higher when the response to clomiphene was positive than when it was negative ($p = 0{\cdot}0005$), but they were intermediate when the response to clomiphene was impaired there being no significant difference between this group and the other two groups.

Table III (a, b and c) shows close relations between the results of clinical assessment of oestrogen state, progestogen challenge and treatment with clomiphene ($p < 0{\cdot}001$ in all cases). For practical purposes the number of cells in the contingency tables can be reduced from nine to four as shown. The categories of oestrogen appearance and response to progestogen have been reduced according to their relation to E_2 values (see above), and the categories of response to clomiphene have been reduced to meet the clinical need to distinguish only between fertile and infertile responses.

There were 38 patients with a positive response to progestogen who were treated with clomiphene in an initial daily dose of only 50 mg. Of these 15 ovulated (39 per cent). Of the remainder, 16 were re-treated with clomiphene, 100 mg daily, and six ovulated (38 per cent); nine who failed to ovulate were treated again

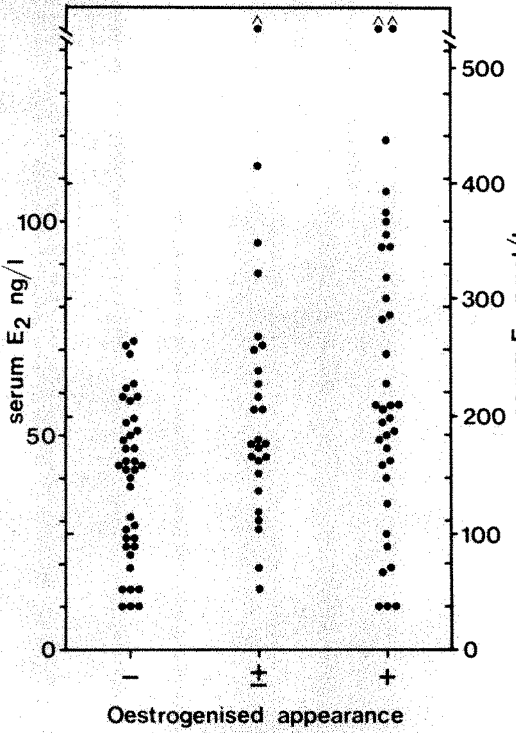

FIG. 1
Serum oestradiol-17β (E_2) concentrations according to the appearance of oestrogen state on clinical examination of the lower genital tract: oestrogen deficient (−), uncertain (±) or oestrogenized (+).

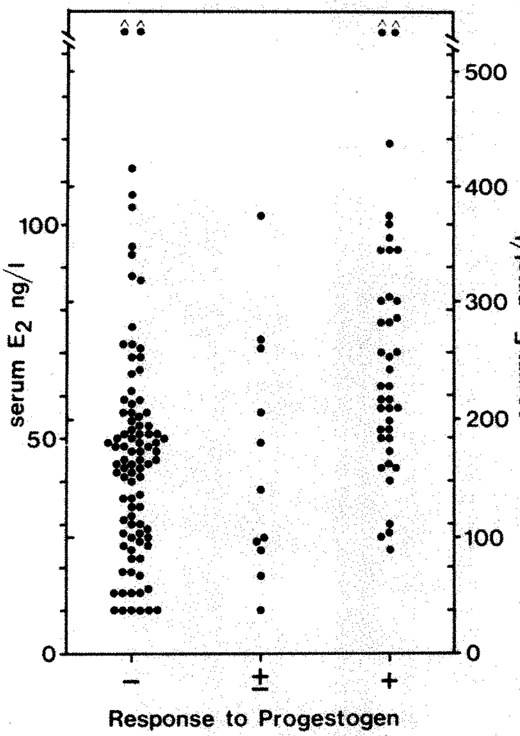

FIG. 2
Serum oestradiol-17β (E_2) concentrations according to the response to a progestogen challenge: negative (−), impaired (±) or positive (+).

TABLE III

Contingency tables showing the relation between the clinical appearance of oestrogen state and (a) the response to progestogen (167 patients), and (b) the response to clomiphene (139 patients). Table (c) shows the relation between the responses to progestogen and clomiphene (182 patients). Symbols as in Figures 1, 2 and 3. In tables (b) and (c) the totals in each of the 4 cells are ringed

Oestrogen appearance	Response to progestogen −	±	+
−	58	8	3
±	35	5	4
+	17	4	33

(a)

Oestrogen appearance	Response to clomiphene −	±	+
−	43 (52)	9	①
±	21	14	2
		(73)	⑬
+	29	9	11

(b)

Response to progestogen	Response to clomiphene −	±	+
−	87	28	5
	(126)		⑤
±	6	5	0
+	11 ㉓	12	㉘

(c)

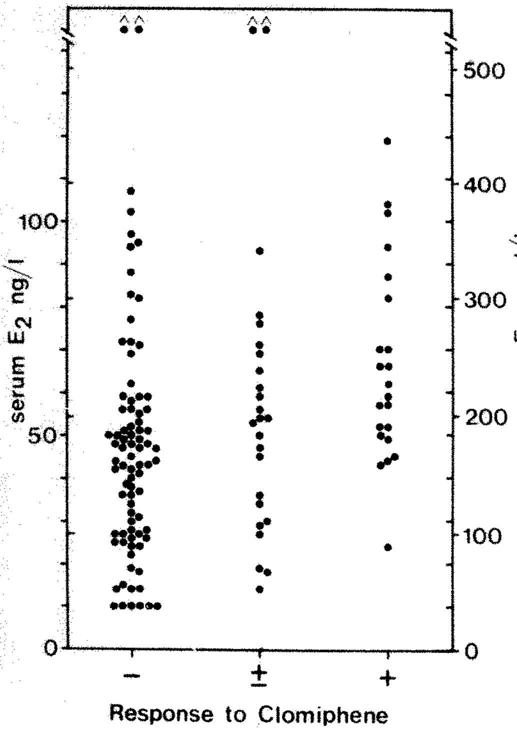

FIG. 3

Serum oestradiol-17β (E_2) concentrations according to the response to clomiphene: negative (−), impaired (±) or positive (+).

and three ovulated (33 per cent). Thus if all patients with a positive response to progestogen were treated with clomiphene for up to 3 cycles, 75 per cent would eventually ovulate. Of the six oestrogenized patients who persistently failed to ovulate there were two with primary ovarian failure, but one of these had 'resistant ovaries' (that is, containing plentiful follicles seen at biopsy but unresponsive to large doses of exogenous gonadotrophins, and subsequently resolving spontaneously with resulting pregnancy) and the other had an ovarian oestrogen secreting tumour (the removal of which led to demonstrable oestrogen deficiency). Of 11 patients without primary ovarian failure who had a negative response to progestogen and a negative or impaired response to an initial course of clomiphene 100 mg daily, none ovulated after three cycles of treatment with clomiphene.

DISCUSSION

While exact definition of oestrogen state in a woman remains elusive it obviously depends on the serum E_2 concentration, which by correlation confirms that visual assessment and the progestogen challenge test both provide means of determining the oestrogen state (Figs. 1 and 2). Correlation of the responses to progestogen with serum E_2 concentrations has also been found by Kletsky *et al* (1975) and Horsky *et al* (1975).

The most important finding in this study was the value of the progestogen challenge test in predicting the response to clomiphene. Our results indicate that when absent or only scanty bleeding occurs after progestogen, there is only a 4 per cent chance of ovulation with clomiphene (5/131, Table IIIc), and the likelihood of increasing this by repeated treatment with clomiphene is negligible, a conclusion supported by Lunenfeld and Insler (1978). On the other hand, normal menstrual bleeding induced by progestogen indicates a 39 per cent chance of ovulation in the first cycle of treatment with only 50 mg daily dosage of clomiphene, this proportion rising to 55 per cent if 100 mg is used (28/51, Table IIIc), and to 75 per cent after treatment for three cycles. The clear conclusion is that it is always worth pursuing treatment with clomiphene in infertile amenorrhoeic women who menstruate normally after a progestogen challenge, but not otherwise. Furthermore, in these patients, it is worth starting with only a 50 mg daily dose of clomiphene in order to minimize the risks of side-effects (mild ovarian hyperstimulation and an 8 per cent chance of multiple pregnancy; Merrell, 1976).

While the correlation of the responses to progestogen challenge and to clomiphene is often described, we can find only two previous and much smaller studies quantifying the correlation, and the findings were similar to ours except that they suggested a better prediction of ovulation (Southam, 1965; Goldenberg *et al*, 1973). However, these authors may have over-diagnosed ovulation by using biological criteria. This is also the probable explanation (Hancock and Oakey, 1973; Hull *et al*, 1979) for the disappointing conception rates previously reported in such patients.

Amongst the individual amenorrhoeic disorders, oestrogen deficiency is particularly notable in hyperprolactinaemia (Jacobs *et al*, 1976) and in the hypothalamic disorders characterized by weight loss and psychological disorder (Knuth *et al*, 1977) (Table II). Kase *et al* (1972) have also reported mainly negative responses to progestogen in a small group of amenorrhoeic women with galactorrhoea and presumed hyperprolactinaemia.

Oestrogenization was notable in three patients with primary ovarian failure (Table II), and the causes in the two who had ovarian biopsy were respectively the resistant ovary syndrome and an oestrogen-secreting tumour. The recognition of these possibilities in patients with elevated serum FSH concentrations thus seems to be the only critical diagnostic need for determining oestrogen state in amenorrhoea. Demonstration of oestrogen deficiency may, however, by use of the progestogen challenge test provide a simple and reliable screening method for distinguishing those women with serious or permanent disorders (Table II) requiring specialist investigation (Hull and Jacobs, 1979).

We found that E_2 values were ranged too widely to provide any useful discrimination between the various amenorrhoeic disorders (Table II), nor were they helpful in predicting the response to clomiphene except that values below 150 pmol/l (41 ng/l), which occurred in a quarter of our patients, were only rarely associated with an ovulatory response to clomiphene (2 per cent; Fig. 3).

Our findings for clinical assessment of oestrogen state indicate that an appearance of oestrogen deficiency allows reliable prediction of failure to ovulate with clomiphene (only 2 per cent; Table IIIb), but otherwise is not helpful. Furthermore, special experience is required to distinguish oestrogen deficiency with confidence.

In conclusion, of the three methods that we studied for determining the oestrogen state of amenorrhoeic women, the progestogen challenge test was clearly the most useful.

ACKNOWLEDGEMENTS

We thank Dr Stephen Franks, Mr E. J. Fox and the Departments of Chemical Pathology at St Mary's Hospital, London and at Southmead Hospital, Bristol for hormone assays; and we are grateful to the University Department of Community Health, Bristol, for help in analysing the data.

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THE EFFECT OF AN INJECTABLE PROGESTOGEN CONTRACEPTIVE ON BLOOD COAGULATION AND FIBRINOLYSIS

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Summary

In 26 women receiving either medroxyprogesterone acetate (Depo-Provera) injections or combined oestrogen-progestogen pills for contraception, tests of coagulation and fibrinolysis were performed before treatment, and after 8, 16 and 24 weeks of therapy. In the medroxyprogesterone group no significant changes were induced in fibrinogen, the vitamin K-dependent factors, or antithrombin III. Plasminogen levels fell during therapy, and were significantly lower than pre-treatment values after 16 and 24 weeks. By contrast, the 13 women receiving oral contraceptives showed raised levels of fibrinogen and plasminogen after 8 weeks of treatment, and of factors VII and X after 24 weeks. These data suggest that medroxyprogesterone acetate injections induce fewer changes in the blood coagulation system than oral contraceptives.

As an injectable contraceptive, medroxyprogesterone acetate (Depo-Provera) has advantages over combined oestrogen/progestogen oral contraceptives for women who find difficulty in remembering to take a pill regularly (Wilson, 1976). Medroxyprogesterone acetate has not yet been recommended for long-term use because it has not been shown to be free from side effects (Seymour and Powell, 1970; Mackay *et al*, 1971).

The use of combined oral contraceptives is associated with a slightly but significantly increased risk of thromboembolism (Vessey and Doll, 1969), and, most likely, it is oestrogen which forms the harmful component of the oral contraceptive (Inman *et al*, 1970). Progestogens differ in the amount of oestrogen-like activity which they exhibit, and this study compares the effects of medroxyprogesterone acetate injection and combined oral contraceptives on the blood clotting mechanisms.

PATIENTS AND METHODS

Two groups of 13 women were studied, after giving informed consent. The first group received 200 mg of medroxyprogesterone acetate

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(Depo-Provera, Upjohn Ltd.) intramuscularly at the start and after 16 weeks of the study. The mean age of this group was 22 years; one patient was nulliparous and 12 were parous. Patients in this group could not, or would not, use oral contraceptives or intrauterine devices, either because of previous failures or unacceptable side effects. They also tended to live mainly in deprived areas, and were poor attenders at clinics. The second group was given combined oestrogen/progestogen oral contraceptives containing 0·03 mg ethinyl oestradiol and either 0·25 mg or 0·15 mg D-norgestrel (Eugynon 30 or Microgynon 30, Schering Chemicals Ltd.) on a standard cyclical regime of three weeks' treatment out of four. The mean age of this group was 19 years; one patient was nulliparous and 12 were parous.

Coagulation tests were made on each patient before treatment and again after 8, 16 and 24 weeks of therapy. Blood (9 ml) was collected by clean venepuncture and mixed with 1 ml 3·8 per cent (w/v) tri-sodium citrate. Platelet free plasma was obtained by centrifugation at 2000 *g* for 15 minutes, and stored at −80 °C until required. The tests performed measured factors II and VII (Owren and Aas, 1951), factor IX (Breckenridge and Ratnoff, 1962) and factor X (Denson, 1961); fibrinogen was measured by a thrombin-clotting time method using the Dade Fibrometer (Becton Dickinson Ltd.), plasminogen was measured by the caseinolytic method of Remmert and Cohen (1949), and antithrombin III by single radial immunodiffusion (Fagerhol and Abildgaard, 1970). Significance tests were performed using a paired Student's t-test, comparing values before treatment with those during therapy.

RESULTS

Patients receiving medroxyprogesterone acetate injections (Table I)

In respect of factors II, VII, IX and X, fibrinogen and antithrombin III, there were no significant changes during medroxyprogesterone acetate therapy. The pre-treatment mean value of factor X was elevated (152 per cent) due to four of the thirteen patients having unexpectedly high concentrations, but these had reverted to normal after 8 weeks. There was a progressive fall in the mean plasminogen level during medroxyprogesterone treatment, and this was significantly less than the pretreatment value at both 16 and 24 weeks ($2P < 0{\cdot}02$ and $2P < 0{\cdot}001$, respectively).

Patients receiving oral contraceptives (Table II)

The mean values of all the vitamin K-dependent clotting factors tended to rise during oestrogen-progestogen therapy, and in respect of factors VII and X were significantly higher at 24 weeks than before treatment ($2P < 0{\cdot}02$ and $2P < 0{\cdot}05$, respectively). Both fibrinogen and plasminogen levels were raised at 8 weeks compared with pre-treatment values ($2P < 0{\cdot}05$ and $2P < 0{\cdot}001$, respectively), but these levels were not maintained and returned to pretreatment values at 16 and 24 weeks. The mean antithrombin III

TABLE I

Effect of medroxyprogesterone acetate (Depo-Provera) injections on the coagulation/fibrinolytic system in 13 patients

Coagulation tests	Weeks of treatment 0	 8	 16	 24
	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD
Factor II (% normal)	121 ± 30	109 ± 33	119 ± 37	118 ± 28
Factor VII (% normal)	109 ± 39	104 ± 41	101 ± 19	112 ± 25
Factor IX (% normal)	129 ± 53	132 ± 36	122 ± 25	120 ± 41
Factor X (% normal)	152 ± 67	123 ± 34	131 ± 34	119 ± 30
Fibrinogen (g/l)	3·15 ± 1·12	3·72 ± 1·42	2·71 ± 0·49	3·33 ± 0·85
Plasminogen (casein units/ml)	2·2 ± 0·6†*	2·0 ± 0·4	1·7 ± 0·4†	1·6 ± 0·3*
Antithrombin III (mg/l)	300 ± 48	313 ± 47	296 ± 54	290 ± 32

(†$2P < 0{\cdot}02$; *$2P < 0{\cdot}001$)

TABLE II

Effect of oestrogen-progestogen oral contraceptives (0·03m g ethinyl oestradiol+0·15 mg or 0·25 mg D-norgestrel) on the coagulation/fibrinolytic system in 13 patients

	Weeks of treatment			
Coagulation tests	0	8	16	24
	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD
Factor II (% normal)	112 ± 23	127 ± 28	106 ± 27	113 ± 28
Factor VII (% normal)	86 ± 16†	74 ± 17	90 ± 35	101 ± 31†
Factor IX (% normal)	125 ± 32	138 ± 45	116 ± 17	128 ± 39
Factor X (% normal)	107 ± 40††	138 ± 46	103 ± 27	141 ± 33††
Fibrinogen (g/l)	2·92 ± 1·89††	3·94 ± 1·21††	3·14 ± 1·41	2·82 ± 0·51
Plasminogen (casein units/ml)	2·0 ± 0·5*	2·8 ± 0·4*	2·2 ± 0·4	2·0 ± 0·3
Antithrombin III (mg/l)	300 ± 40	305 ± 36	279 ± 42	292 ± 57

(†2P < 0·02; ††2P < 0·05; *2P < 0·001)

level was lower than the pre-treatment value at 16 and 24 weeks, but the difference fell just short of statistical significance.

DISCUSSION

Injectable progestogens represent a useful additional contraceptive method to those already available, although they have not yet been made available for long term use because of continuing doubts about their safety. One of the major risks of conventional combined oestrogen-progestogen oral contraceptive therapy is the thrombosis which is associated with well documented changes in coagulation mechanisms. The characteristic changes associated with oral contraceptive therapy are raised levels of factors VII and X (Poller and Thomson, 1966), raised plasminogen and fibrinogen (Hedlin, 1975), and reduced antithrombin III (Howie *et al*, 1970). In this study, in which low dose oestrogen pills were used, these changes were confirmed. Since the low-dose pills were able to induce similar changes to those containing 50 μg of oestrogen, it is possible that reducing the oestrogen dose below 50μg will not have a material impact on the thrombosis risk.

The patients receiving medroxyprogesterone acetate injections showed none of the coagulation changes associated with conventional oral contraceptive therapy. The only significant change to occur in this group was a progressive fall in plasminogen, which is the reverse of the trend found during oral contraceptive therapy. The significance of this fall is difficult to interpret, but it might possibly indicate a reduced fibrinolytic capacity in such women. The overall absence of coagulation changes is in keeping with other reports which have studied the effects of oral progestogen-only contraceptives (Poller *et al*, 1969; Mink *et al*, 1972). Baele *et al* (1974) have reported a decrease in the level of factor II after seven months' parental administration of medroxyprogesterone acetate, but our study did not confirm this finding. The results from this study would suggest that, on balance, medroxyprogesterone acetate injections would be less likely to induce a thrombosis than combined oestrogen-progestogen oral contraceptives.

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THE EFFECT OF MENOPAUSAL STATUS AND SEQUENTIAL MESTRANOL AND NORETHISTERONE ON SERUM CHOLESTEROL, TRIGLYCERIDE AND ELECTROPHORETIC LIPOPROTEIN PATTERNS

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Summary

The serum cholesterol, trigylcerides and electrophoretic lipoprotein patterns of 35 postmenopausal women, who subsequently received sequential mestranol and norethisterone, were compared with those of 35 premenopausal women of the same age and weight. The postmenopausal women had a significantly higher level of serum cholesterol ($p < 0{\cdot}01$) than the premenopausal women, and a significant reduction ($p < 0{\cdot}001$) occurred in this group after two months of therapy. There was no significant difference in level of serum cholesterol between the premenopausal group and the postmenopausal group receiving sequential mestranol and norethisterone for two months. The serum triglycerides were not significantly higher in the postmenopausal group but there was a significant increase ($p < 0{\cdot}001$) after two months of therapy. The marked alteration in lipid levels at the menopause may in part account for the great increase in coronary artery disease in postmenopausal women but whether these changes are reversible by giving hormone therapy remains speculative.

INCREASED serum cholesterol levels are regarded as an import risk factor for cardiovascular disease in individual patients, but the effect of alterations in serum triglyceride levels on morbidity and mortality from cardiovascular disease is less well understood. The incidence of cardiovascular disease increases in postmenopausal women and this increase may be related to the well documented elevation in serum lipid concentrations (Hallberg *et al*, 1966). Oestrogen therapy is widely prescribed for the relief of climacteric symptoms but the possible long-term effects on the incidence of cardiovascular disease have not been established. In younger women receiving combined oestrogen and progestogen oral contraceptives there is strong evidence of an increased risk of cardiovascular disease over the age of 35 years and especially when associated with cigarette smoking, obesity and a family history of the disease (Beral, 1977; Vessey *et al*, 1977). It is not known whether these findings can be extrapolated to the postmenopausal woman who is receiving a lower oestrogen dose.

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Age-related changes in serum lipids have been demonstrated in previous studies (Johnson *et al*, 1965; Hallberg *et al*. 1966; Boyns *et al*, 1969). In this study we have assessed the effect of menopausal status and oestrogen therapy on lipid values in women of the same age and weight; and the implications concerning cardiovascular disease are discussed.

PATIENTS AND METHODS

Serum was obtained from fasting women attending the menopause clinic of the Birmingham and Midland Hospital for Women. Of the women not receiving oestrogens during the previous two months, 35 premenopausal women were matched for age with a group of 35 postmenopausal women, so that each premenopausal woman was paired with a postmenopausal one of the same age. All the premonopausal women had regular periods and a serum follicle stimulating hormone (FSH) concentration within a normal premenopausal range of less than 10 Iu/l (Shaw, 1976). The FSH was determined by a standard double antibody radioimmunoassay (Lynch and Shirley, 1975). The postmenopausal women had amenorrhoea of at least a year and a serum FSH concentration greater than 20 Iu/l. The postmenopausal women were then given sequential mestranol and norethisterone (Syntex Menophase) for two months and a further specimen of serum obtained. Cholesterol (Levine and Zak, 1964) and triglyceride assays (Kessler and Lederer, 1966) and lipoprotein electrophoresis on agarose gel (Noble, 1968) were performed on all three groups. The lipoprotein electrophorectograms were typed according to the Fredrickson/WHO classification (Beaumont *et al*, 1970).

Statistical significance of the results was assessed by either Wilcoxon's rank sum tests or the chi-squared test of association.

RESULTS

The mean age of the women in both groups was 44·2 years (range 37 to 51 years). The serum cholesterol and triglyceride results are shown in Figures 1 and 2 respectively. In Table I, the means and ranges of the serum cholesterol, triglyceride and weight in the three groups are compared.

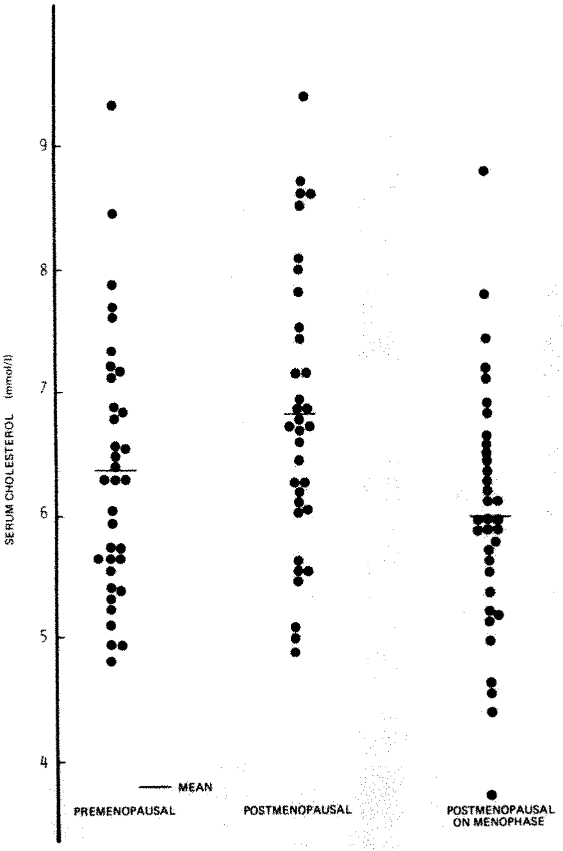

FIG. 1

Scatter diagram comparing the serum cholesterol concentrations of 35 age matched premenopausal women, with 35 postmenopausal women, both before, and after two months of sequential mestranol and norethisterone.

The mean serum cholesterol concentration was significantly greater in the untreated postmenopausal women as compared with the premenopausal women ($p < 0{\cdot}01$). There was also a significant reduction in serum cholesterol in the postmenopausal women receiving sequential mestranol and norethisterone ($p < 0{\cdot}001$). There was no significant difference in serum cholesterol

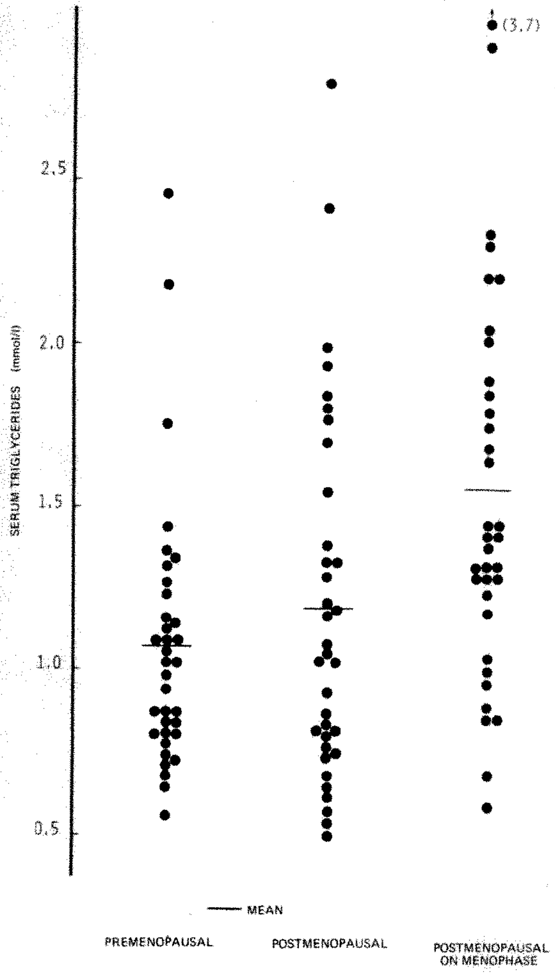

FIG. 2

Scatter diagram comparing the serum triglyceride concentrations of 35 age matched premenopausal women, with 35 postmenopausal women, both before, and after two months of sequential mestranol and norethisterone.

between the premenopausal group and the postmenopausal group receiving sequential mestranol and norethisterone.

There was no significant difference in the serum triglyceride concentration between the premenopausal and untreated postmenopausal women, although the mean values in the latter group were slightly higher. There were only two women in the premenopausal group, but six in the postmenopausal group, with a serum triglyceride concentration of greater than 1·8 mmol/l (upper limit of normal range). After two months of sequential therapy there was a significant increase in serum triglyceride concentration ($p < 0\cdot001$). There was a statistically significant difference ($p < 0\cdot05$) between the premenopausal group and the postmenopausal group receiving sequential mestranol and norethisterone and ten patients in the latter group had a serum triglyceride concentration of greater than 1.8 mmol/l.

When comparing the lipoprotein electrophoresis results (Table II), there was a significant difference between the premenopausal and postmenopausal groups. Constructing a fourfold table between the normal and abnormal types in the premenopausal and postmenopausal groups, there was a significant increase in the number of abnormal electrophoretic strip types in the postmenopausal group ($\chi^2 = 4\cdot48$; $p < 0\cdot05$). There was also a difference between the premenopausal group and the postmenopausal group receiving therapy but this was not statistically significant ($\chi^2 = 3\cdot54$; $0\cdot1 > p > 0\cdot05$). Therapy caused a reduction in the number of patients with type II hyperlipidaemia with an equivalent increase in type IV hyperlipidaemia.

There was no difference in the mean weight of the premenopausal women and the postmenopausal women, either before, or after treatment.

DISCUSSION

This study indicates that the menopause, independent of age and weight, is an important factor in serum lipid levels. In the postmenopausal group there is a higher level of serum cholesterol and triglyceride concentration, and an increase in the number of patients with abnormal electrophoretic lipoprotein patterns. Previous studies have shown that serum cholesterol increases with age (Johnson *et al*, 1965; Hallberg *et al*, 1966; Boyns *et al*, 1969). The last two studies showed that triglycerides also increased with age but the association was less marked than with cholesterol. None of these studies related to the menopausal status of the patients. Hallberg and Svanborg (1967) compared the cholesterol and triglyceride status in groups of 50-year-old premenopausal and postmenopausal women and found a significantly higher level of both lipids in the postmenopausal group. However, the two groups were not carefully matched; for example, their weights were

TABLE I

Serum cholesterol, triglycerides and weight in age matched premenopausal women and postmenopausal women before and after two months of sequential mestranol and norethisterone

	Serum cholesterol mmol/l		Serum triglycerides mmol/l		Weight (kg)	
	Mean	Range	Mean	Range	Mean	Range
Premenopausal women	6·34	4·80–9·32	1·08	0·56–2·47	62·5	50–81·5
Postmenopausal women	6·85	4·9–9·43	1·21	0·50–2·81	60·9	53·5–81
Postmenopausal women receiving therapy	6·03	3·75–8·80	1·58	0·60–3·70	59·9	54–80·5

TABLE II

Electrophoretic strip types (Frederickson/WHO Classification) in age matched premenopausal women and postmenopausal women before and after two months of sequential mestranol and norethisterone

	Strip type				
	Normal	IIA	IIB	IV	Total
Premenopausal women	29	4	1	1	35
Postmenopausal women	21	7	5	2	35
Postmenopausal women receiving therapy	22	1	4	8	35

significantly different. Utian (1972) showed that oophorectomy had little effect on cholesterol metabolism but the number of patients was small and the women may not have been of the same age and weight.

Compared with their male counterparts, premenopausal women have a lower incidence of coronary artery disease which may partly be related to their lower level of serum cholesterol. Sznajderman and Oliver (1963) showed that women who had a premature menopause had a higher incidence of coronary artery disease and elevated serum cholesterol than their premenopausal counterparts. In a series of 145 women with ischaemic heart disease under the age of 45, it was found that 20 per cent of them had a premature menopause (Oliver, 1974). Hypercholesterolaemia was the most important associated factor, but raised blood pressure and cigarette smoking were risk factors. In the Framingham study (Kannel *et al*, 1971), it was demonstrated that the closing of the gap between the sexes in the incidence of coronary artery disease with age could be attributed to the steady rise in lipid levels in women beyond the age of 30 years. Men appeared to reach their peak at this age with little increase thereafter.

The majority of studies relating lipid status to coronary artery disease have been on men and have shown that serum cholesterol is the most useful predictor of coronary artery disease (Wilhelmsen *et al*, 1973; Kannel, 1976; Rosenman *et al*, 1976). These studies also indicated that serum triglycerides showed a negligible association with the incidence of coronary artery disease. However, Pelkonen *et al* ((1977) and Carlson and Bottiger (1972) showed an association between increased triglyceride levels and coronary artery disease but only Pelkonen *et al* (1977) used multivariant analysis techniques. In his series, there was no association in these patients with a serum triglyceride level of less than 1·7 mmol/l but a highly significant one in those patients with a level of greater than 1·7 mmol/l. In our study 3 out of 35 premenopausal patients and 8 out of 35 postmenopausal patients had serum triglyceride levels of greater than 1·7 mmol/l.

Serum cholesterol is one of the associated factors in coronary artery disease (Kannel, 1976) and a significant elevation in level after the menopause which is not solely related to age is important. Not only are the serum cholesterol and triglyceride levels higher in postmenopausal women but the number of patients with abnormal electrophoretic strip patterns is significantly greater than the premenopausal controls (Table II). The change affects type IIA and IIB reflecting an increase in low density lipoproteins, which are composed of 50 per cent cholesterol, 15 per cent triglyceride and 35 per cent phospholipid (Castelli and Moran, 1971). These types are particularly associated with coronary artery disease (Kannel, 1976).

The premenopausal controls, although attending a menopausal clinic, accurately reflect the levels of serum cholesterol and triglyceride found in the general premenopausal population. The levels in the various age groups were the same as that found by Magnani and Moore (1976) in a general population using the same laboratory.

The reduction of serum cholesterol in postmenopausal women resulting from sequential mestranol and norethisterone could be beneficial but the concurrent increase in serum triglyceride is difficult to interpret as a risk factor. Although the level of serum triglyceride was significantly increased, the number of patients with a level of greater than 1·8 mmol/l (upper limit of normal range) was only increased from six to ten. As can be seen from Table II, there is an increase in the number of patients with type IV hyperlipidaemia among those receiving mestranol and norethisterone with a corresponding reduction in the number with type IIA hyperlipidaemia. Type IV is often associated with a disordered carbohydrate metabolism and it has already been shown that patients receiving mestranol and norethisterone have a reduction in carbohydrate tolerance (Sturdee *et al*, 1976; Thom *et al*, 1977).

Whether a reduction in serum cholesterol will result in a reduction in the incidence of coronary artery disease is by no means proven although the results of Turpeinen *et al* (1968) were suggestive of this.

There is no doubt that there is a marked alteration in lipid metabolism at the menopause but whether by giving oestrogens and progestogens there will be a reduction in the incidence of coronary artery disease is open to speculation. Long term epidemiological studies may supply the answer.

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DIAGNOSTIC ACCURACY OF THE MIMARK ENDOMETRIAL CELL SAMPLER IN 101 PATIENTS WITH POSTMENOPAUSAL BLEEDING

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Summary

The efficacy of the MiMark endometrial cell sampler in the cytological assessment of endometrium was evaluated in 101 patients with postmenopausal bleeding. The apparatus was successful in diagnosing all but one of the endometrial carcinomas in the series. Reports of its accuracy in diagnosing endometrial hyperplasia and other endometrial pathology cannot be substantiated.

CERVICAL and vaginal cytology has gained widespread use in identifying intraepithelial carcinoma of the cervix but not of the uterine body (Brush and Taylor, 1975). This had led to the development of further techniques for screening for endometrial pathology, namely aspiration, brush or irrigation techniques (Anderson *et al*, 1976). All of these are expensive, difficult to use or require complicated processing in the laboratory.

Milan and Markley (1973) developed the MiMark endometrial sampler which is inexpensive , simple and produces material which can be processed in much the same way as a cervical smear. We now report on its diagnostic accuracy in women complaining of postmenopausal bleeding.

PATIENTS AND METHODS

We studied 101 women who were referred to the Gynaecological Clinics in the Bath Clinical Area because of postmenopausal bleeding (mean age 57 years; range 45 to 81 years). The patients were consecutive but those with carcinoma of the cervix were excluded.

A history was taken and general and pelvic examinations were made, cervical smears were taken and arrangements were made for admission to hospital for examinaion under anaesthesia and curettage. Just before currettage and under anaesthesia, samples were taken for cytology from the posterior vaginal fornix and from the endometrial cavity using the MiMark sampler.

The MiMark endometrial sampler (Fig. 1) is composed of two disposable sterilised instruments. The first is a loosely wound flat helical spiral of soft inert plastic, 6 cm in length and attached to a thin round handle. The spiral has a semi-sharp edge so that the surface cells are scraped off into the endocervical mucus. The second instrument consists of a curved plastic rod, one end of which serves as a probe and cervical dilator. The other end consists of a flat

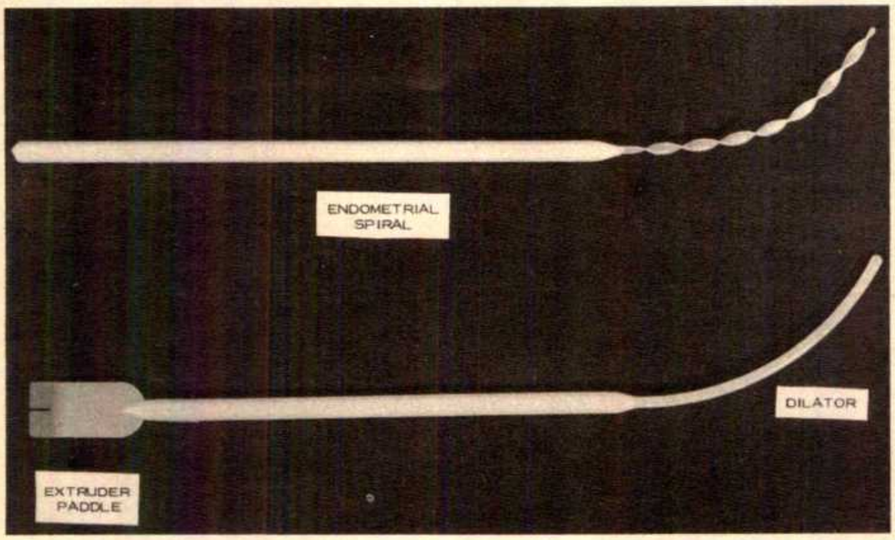

FIG. 1
The MiMark endometrial cell sampler.

extruder paddle with a slit cut into it, the size of the cross sectional diameter of the spiral.

A bimanual pelvic examination was made. It was sometimes necessary to grasp the cervix with a tenaculum and dilate the external os with the plastic dilator. The spiral was then introduced through the cervix into the uterus and rotated six to ten times. In order to obtain an adequate sample including the cervical mucus the spiral was rotated as it was withdrawn.

The proximal end of the spiral was then placed in the slot in the extruder paddle and gently twisted through to strip off the endometrial tissue and mucus. The material was then spread evenly on a glass slide and fixed immediately with industrial methylated spirit 74^{op}. Any material left on the paddle was put into 10 per cent formal saline and processed through wax embedding to sections stained with the standard Papanicolaou technique.

The material from the MiMark sampler, the posterior fornix and the cervical smear were initially examined without knowledge of the histology of the curettings. On completion of the study, the slides were reviewed to establish reasons for discrepancies between histological and cytological diagnosis.

RESULTS

Table I shows the histological diagnosis obtained after endometrial curettage. The diagnosis of the malignant tumours was confirmed at laparotomy. The ovarian carcinoma was adherant to the uterus and had invaded the myometrium.

In the group of nine patients with endometrial adenocarcinoma, smears from the MiMark sampler showed malignant cells in six patients, suspicious cells in two patients and no malignant cells in one patient. On reviewing the slides the two suspicious smears were thought to be definitely malignant but no malignant cells could be identified in the negative smear. In five patients, the MiMark sampler obtained sufficient material for the histological diagnosis of adenocarcinoma. In two patients, both the cervical and posterior fornix smears showed malignant cells; no other cervical or posterior fornix smears were positive in this group.

In the patient with the mixed mesodermal tumour and the one with the ovarian tumour, endometrial, cervical and posterior fornix smears all contained malignant cells. In the patient with the ovarian tumour, the endometrial samples contained sufficient tissue for a histological diagnosis.

Endometrial cytology was reported as abnormal although benign in four of the eight patients with cystic hyperplasia. In a further two patients the sample contained sufficient

TABLE I

*Histology of endometrial curettings obtained from 101 patients in the study**

Diagnosis	No. of patients
Endometrial carcinoma (one patient also had a polyp)	9
Mixed mesodermal tumour of uterine corpus	1
Ovarian adenocarcinoma	1
Atypical hyperplasia	3
Cystic hyperplasia	8
Endometrial polyp	17
Normal premenopausal endometrium	3
Normal postmenopausal endometrium (or no curettings)	60

* For comments on cytological and MiMark sampler findings see text.

material for a histological diagnosis of cystic hyperplasia and sufficient in one for a diagnosis of proliferative but not hyperplastic change. The specimens obtained by MiMark endometrial sampler thus showed endometrial activity in seven patients. Retrospective analysis did not alter these figures.

Only one of the three patients with atypical endometrial hyperplasia had abnormal endometrial cytology. One of the endometrial samples contained a small amount of tissue which showed only proliferative activity on histology. The other two patients were reported as normal and the diagnosis was not revised on reviewing the slides. Cervical and posterior fornix cytology were of no value in this group.

Endometrial cytology was benign in 16 of the patients with endometrial polyps. Malignant cells were found in endometrial cytology in one patient but she had a coexistent endometrial carcinoma.

Endometrial cytology was reported as benign in three patients with normal premenopausal endometrium and in two of them there was sufficient material for a histological diagnosis. Of the 60 patients with inactive postmenopausal endometrium, two had malignant and five had suspicious endometrial cytology. On reviewing these slides we considered that the error was invariably due to misinterpretation of artifact.

DISCUSSION

The MiMark endometrial sampler led to the detection of malignancy in 10 of the 11 patients affected. Cervical and vaginal cytology identified only four of these patients. There was also sufficient material for histological diagnosis in five patients. We think the incidence of false positives would diminish with greater experience.

We agree with Paterson and Sturdee (1978) that the diagnosis of endometrial hyperplasia requires a technique, such as Vabra aspiration, that consistently produces material suitable for histology. The MiMark sampler only produced such material in 6 of 11 patients with endometrial hyperplasia.

The MiMark sampler cannot be recommended as the only diagnostic test in patients with postmenopausal bleeding, nor does it seem likely that it will be satisfactory to monitor endometrial activity in patients on postmenopausal hormone replacement therapy.

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ACUTE PROLIFERATIVE GLOMERULONEPHRITIS WITH CRESCENTS AND RENAL FAILURE IN PREGNANCY SUCCESSFULLY MANAGED BY INTERMITTENT HAEMODIALYSIS

CASE REPORT

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Summary

A 26-year-old patient with no previous history of renal disease developed acute non-streptococcal crescentic glomerulonephritis with severe renal failure in the 17th week of her second pregnancy. It became necessary to treat her with haemodialysis to maintain the blood urea around 25 mmol/l. The haemoglobin was maintained above 9 g/dl with regular blood transfusions and the blood pressure was controlled with hypotensive drugs. Measurement of fetal biparietal diameter and human placental lactogen indicated normal fetal growth and placental function. The patient spontaneously delivered a healthy infant at 32 weeks. Haemodialysis requirements decreased post partum and the patient even managed without dialysis for 12 weeks. Renal function, however, remained severely impaired and maintenance haemodialysis was again necessary at nine months post partum. Glomerulonephritis complicating pregnancy is reviewed and the management of acute and chronic renal failure in pregnancy is discussed.

'ACUTE nephritis' is known to complicate pregnancy and reports include acute streptococcal and non-streptococcal glomerulonephritis and even cases of exacerbation of chronic glomerulonephritis (O'Dwyer and Montgomery, 1954; Kincaid-Smith *et al*, 1967; Nadler *et al*, 1969; Strauch and Hayslett, 1974; Bear 1976). Fetal prognosis is allegedly poor in the presence of severe nephrotic syndrome, marked hypertension and progressive renal failure. Most pregnancies have terminated in either spontaneous or therapeutic abortion (Strauch and Hayslett, 1974). We report the management of a patient who developed non-streptococcal crescentic glomerulonephritis during the second trimester of pregnancy with hypertension, nephrotic syndrome and severe renal failure.

CASE REPORT

A 26-year-old Caucasion woman had an uncomplicated first pregnancy ending in a forceps delivery at 38 weeks in 1975. In that pregnancy, her blood pressure varied between 100/60 mm Hg and 140/70 mm Hg, the haemoglobin was 12·3 g/dl at 36 weeks and there was no proteinuria.

The patient was seen again in August 1977 at 12 weeks gestation when her blood pressure was 130/80 mm Hg, there was no proteinuria and the body weight was 56 kg. She was reviewed at 15 weeks and the blood pressure was found to be 130/70 mm Hg, no proteinuria was detected and the weight had increased to 59 kg. Two weeks later, the patient was admitted to hospital with a blood pressure of 150/100 mm Hg and over 10 g of protein/l of urine (Albustix). During this time she passed dark urine several times and developed ankle oedema and facial swelling. There was no history of arthralgia, sore throat or skin rashes. The blood urea was 19·5 mmol/l, creatinine 0·40 mmol/l, haemoglobin 7·4 g/dl and creatinine clearance 12 ml/minute. Twenty-four hour urine protein excretion varied between 2 to 4·5 g and was of low selectivity, the serum albumin being 26 g/l. The urinary sediment contained numerous red blood cells and red blood cell casts. There was no evidence of disseminated intravascular coagulation, the concentration of serum fibrin degradation products being less than 10 μg/ml. The auto-immune profile, complement levels and anti-streptolysin 0 titre were normal.

Initial management of the patient consisted of a 40 g protein diet with sodium and potassium restriction and blood transfusion. Methyldopa, 250 mg four times daily, was necessary to reduce diastolic blood pressure to less than 90 mm Hg. However, three weeks later, the blood urea had risen to 29·7 mmol/l and the creatinine to 0·52 mmol/l. A single shot nephrogram showed that both kidneys were of normal size and shape. An open renal biopsy was done because of limited local experience with needle biopsy in pregnant patients and histological examination showed severe proliferative glomerulonephritis. There were at least 60 glomeruli of which 11 showed extensive ceollular degeneration. Two-thirds of the remaining glomeruli showed prominent epithelial crescents, an increase in mesangial matrix and moderate mesangial cell proliferation. Most capillary lumina were not patent and there was slight irregular thickening of the basement membrane. Immunofluorescence showed a granular deposit of IgA in the glomeruli with a homogenous deposit in the walls of interlobular arteries. A granular deposit of C3 was also present in glomeruli and tubular basement membrane. These findings confirmed immune complex nephritis. Electron microscopic examination showed intra-membranous, subendothelial and mesangial electron dense deposits.

Intermittent haemodialysis was started at 20½ weeks gestation for two 9-hour sessions weekly (Fig. 1) using a one square metre Ultraflow II coil dialysis system. Heparin 5000 units subcutaneously twice daily was given to maintain shunt patency. The patient was maintained on an 80 g protein diet with vitamin supplements (ascorbic acid, aneurine Co. forte, folic acid and ferrous sulphate). Salt and water intake was not restricted. She was transfused as necessary to maintain a haemoglobin of 8 to 11 g/dl. The frequency of dialysis was increased to three times per week (total 24 hours per week) and subsequently to 26 and 30 hours weekly to keep the blood urea below 30 mmol/l (Fig. 1). There was a progressive rise in serum creatinine during the pregnancy and creatinine clearance, estimated using the urine collected in the immediate 24 hours prior to haemodialysis, gradually fell to 3 ml/minute.

Ultrasound measurement of the fetal biparietal diameter (BPD) at 21½ weeks gestation was normal at 60 mm. The serum human placental lactogen (HPL) level at 22 weeks was 3·7 mg/l (normal range 1 to 3·5 mg/l). Subsequent estimations of fetal biparietal diameter and serum HPL levels (Fig. 1) indicated normal fetoplacental growth and function. At 32 weeks the patient went into spontaneous labour and delivered a normal 1·54 kg male infant with an Apgar score of 8 at one minute. There were no obstetric or neonatal complications.

Heparin therapy was stopped and intermittent dialysis (two 9-hour sessions) was continued after delivery. Renal function, however, gradually improved and 5 months after delivery the blood creatinine was 0·66 mmol/l, urea 26 mmol/l and creatinine clearance 12 ml/minute. Dialysis was therefore discontinued and the patient maintained on a 40 g protein diet for 3 months. The blood urea level then began to rise and regular dialysis was restarted (14 hours per week). The patient remained well on maintenance haemodialysis and has had a successful kidney transplant. The baby, aged 18 months is heatlhy.

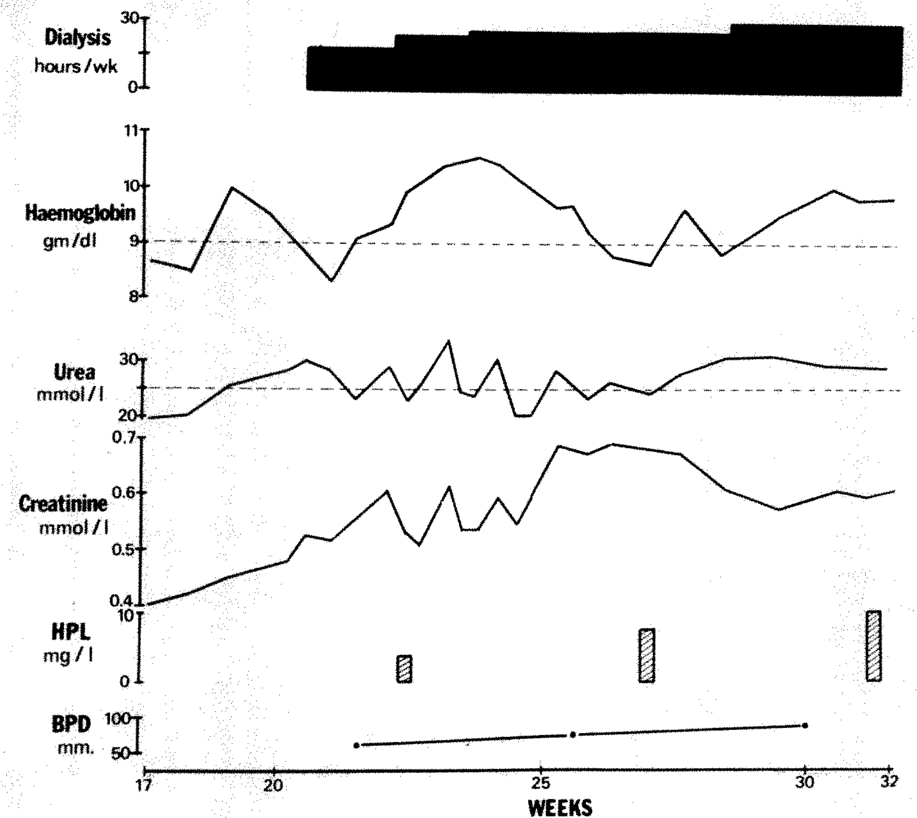

FIG. 1

Fetal biparietal diameter (BPD) and maternal blood levels of haemoglobin, urea, creatinine, human placental lactogen (HPL) during pregnancy. Dialysis hours per week were increased to maintain blood urea around 25 mmol/l (dotted line) and blood transfusions were given to maintain haemoglobin above 9 g/dl (dotted line).

DISCUSSION

'Acute nephritis' has been reported in pregnancy but histological descriptions of the renal lesion are not available in the majority of cases and when renal biopsies were performed, it appears that many patients had exacerbations of a chronic process (Lindheimer and Katz, 1977). Our patient was seen on two occasions prior to admission and at these times no evidence was found to suggest an underlying renal disease. It therefore appears that the renal lesion occurred after the first 12 weeks of pregnancy.

Acute streptococcal and non-streptococcal proliferative glomerulonephritis is rare in pregnancy (Lindheimer and Katz, 1977). Since pregnancy is accompanied by a number of alterations in maternal immune mechanisms (best described as a hyporesponsive state) (Need, 1976) these changes may protect pregnant patients from immune complex nephritis caused by nephritogenic streptococci (Lindheimer and Katz, 1977) or possibly by other antigens. Acute post-streptococcal glomerulonephritis is extremely rare in pregnancy but in those cases where the diagnosis appeared certain (O'Dwyer and Montgomery, 1954; Kincaid-Smith *et al*, 1967; Nadler *et al*, 1969) 5 of the 6 pregnancies ended successfully and renal function returned to normal in all these women. There is only one report of crescentic glomerulonephritis occurring during pregnancy (Strauch and Hayslett, 1974) and the inexorable rapid decline in renal function in this patient was typical of the course of crescentic glomerulonephritis (Bacani *et al*, 1968). Spontaneous abortion occurred in the fourth month of pregnancy and despite this, end stage renal failure necessitating haemodialysis developed within weeks of the termination of pregnancy. The course followed by our patient was similar with rapid progression to end stage renal failure. We would attribute fetal survival to early dialysis and to the achievement of specific objectives for control of haemoglobin, blood urea and serum creatinine.

There is no good evidence that pregnancy causes deterioration of renal function or otherwise affects the rate of progression of established renal lesions beyond what might be expected in the non-pregnant state (Strauch and Hayslett, 1974) although this is disputed (Fairley *et al*, 1973; Kincaid-Smith and Fairley, 1976). In a recent report (Leader *et al*, 1978) pregnancy resulted in deterioration of renal function in a patient with focal glomerulonephritis after a stable period of 9 years. In our patient then, it may be appropriate to question the ethics of prolonging the pregnancy by haemodialysis when it is possible that further deterioration in renal function may have been prevented by early termination of the pregnancy.

The safety of dialysis in pregnancy is now established. It has been used as an adjunct to management of pregnancy in patients who were not at the time of conception being treated with haemodialysis. Such management has been successful in patients with pre-eclampsia (Goldsmith *et al*, 1971) and in a patient in whom severe lupus glomerulonephritis developed for the first time in mid pregnancy and necessitated haemodialysis treatment (Mitra *et al*, 1970). Similar success was obtained when a patient already on maintenance haemodialysis conceived (Sheriff *et al*, 1978). Haemodialysis has also been used to preserve gestation in women in whom acute renal failure has occurred during pregnancy (Nemoto *et al*, 1977). It was also successful in our patient and there was some improvement in renal function after delivery.

The control of blood urea, creatinine and haemoglobin levels and of hypertension is important in patients receiving dialysis treatment during pregnancy. It has been suggested that intrauterine fetal death is likely in patients with renal failure if plasma urea concentration exceeds 21·6 mmol/l for more than a few days (Tenny and Dandrow, 1961); but Sheriff *et al* (1978) have shown that successful pregnancy can be achieved when a blood urea concentration of 25 mmol/l is maintained for several weeks.

Although the prognosis for maternal renal function and fetal survival is poor when severe crescentic glomerulonephritis occurs in pregnancy, a successful outcome to the pregnancy is possible with intermittent haemodialysis. There is no definite evidence to suggest that pregnancy *per se* has a deleterious effect on the natural history of this form of glomerulonephritis and as the course of this disorder is a relentless and rapid progression to end stage renal disease, it would appear that termination of pregnancy is not necessarily indicated.

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HAEMANGIOMA OF THE FALLOPIAN TUBE
CASE REPORT

BY

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Summary

I present the sixth report of a patient with a haemangioma of the Fallopian tube and the first from the United Kingdom, The patient presented with an acute abdomen due to haemoperitoneum.

HAEMANGIOMATA of the Fallopian tube have been reported only five times (Ragins and Crane, 1947; Gusmano, 1951; Talerman, 1969; Patel *et al*, 1972; Ebrahimi and Okagaki, 1973). The present report is the first from the United Kingdom, and the second of a Fallopian tube haemangioma presenting as an acute abdomen with haemoperitoneum.

CASE REPORT

A 24-year-old white woman presented on 25th March, 1978 at King's College Hospital with a history of lower abdominal pain for 12 hours. Her last menstrual period had ended two weeks before admission, the periods being regular with normal duration and quantity. She had a healthy seven-year-old boy and had had one miscarriage. She had suprapubic tenderness. Vaginal examination showed a soft cervix, an intrauterine contraceptive device *in situ* and tenderness in the fornices, which was more marked on the right side than the left. A tentative diagnosis of torsion of an ovarian cyst was made. At laparoscopy on the same day, an excellent view of normal-looking ovaries and tubes was obtained, but there was blood in the pouch of Douglas and so the patient had a laparotomy at which 500 ml of blood was found in the pelvic cavity. Both ovaries and the right tube looked normal, but blood was dripping from the fimbriated end of the left Fallopian tube. A left salpingectomy was therefore done. The patient made an uneventful recovery and was discharged from hospital on 30th March, 1978.

Pathology

The specimen consisted of a Fallopian tube 4·5 cm long and 1·2 cm in diameter in its outer third. There was no localised abnormality on the serosal surface. A blood clot measuring 1 × 1 × 2 cm was seen at the fimbriated end. Slicing showed a lumen dilated with blood clot. Blocks were taken from the ampullary end and from the relatively normal uterine end of the Fallopian tube.

On histological examination, the sections showed a Fallopian tube with a haemangioma in the villi and the adjacent wall of the tube (Figs. 1 and 2). The haemangioma was composed of arterioles and capillaries and extended to the fimbria. The rest of the Fallopian tube was normal.

DISCUSSION

Ragins and Crane (1947) reported a haemagioma 1·5 cm in diameter as an incidental finding in the outer third of the Fallopian tube of a 28-year-old white woman, who had undergone hysterectomy and left salpingo-oophorectomy. Gusmano (1951) found a small Fallopian tube haemangioma at autopsy in a 77-year-old

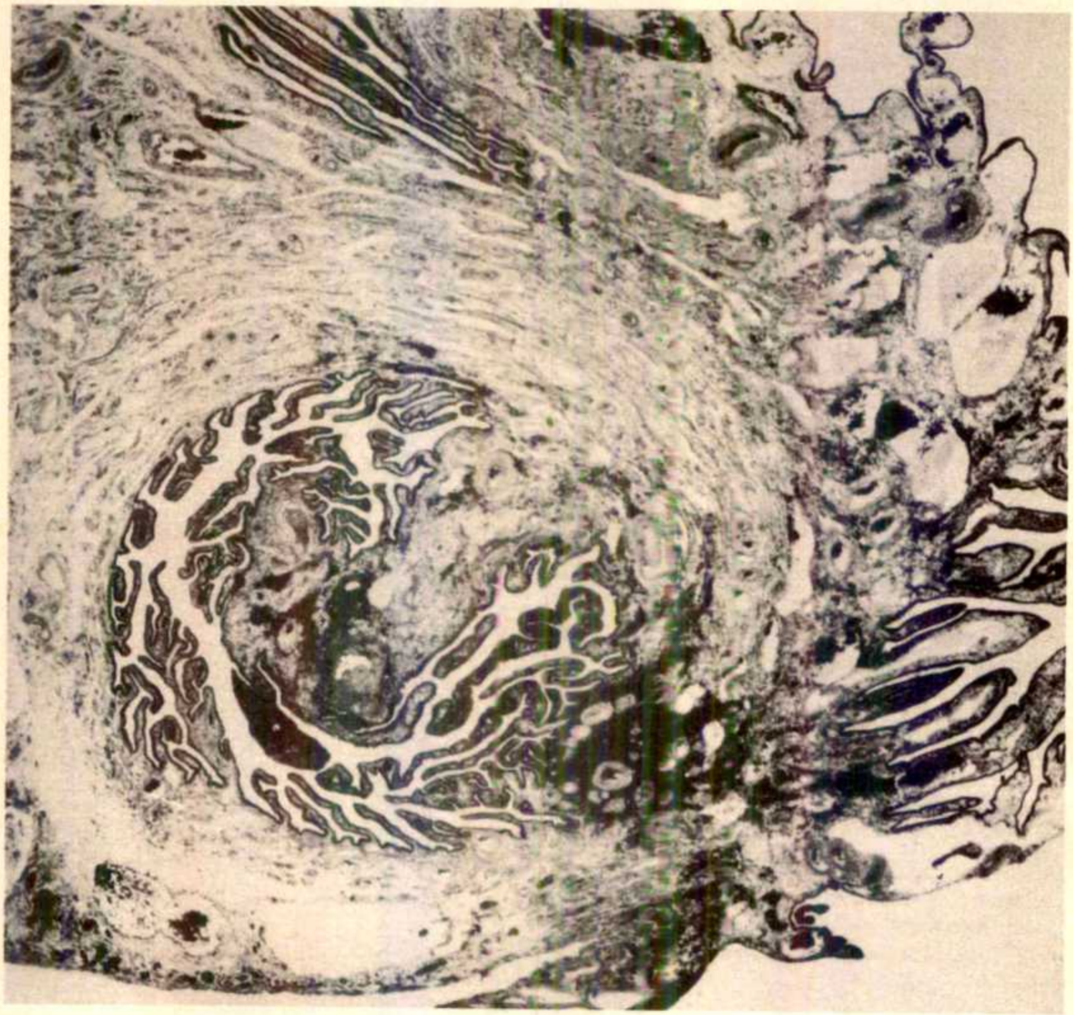

FIG. 1

Fallopian tube with haemangioma (haematoxylin and eosin ×23).

woman dying of meningitis. Talerman (1969) described a Fallopian tube haemangioma in a total hystero-salpingectomy for dysmenorrhea on a mentally-subnormal, 23-year-old negro woman. Patel *et al* (1972) reported a case of cavernous haemangioma with spontaneous rupture. Ebrahimi and Okagaki (1973) found a haemangioma in a surgical specimen from a 66-year-old white woman who had had preoperative radiotherapy and a total hysterectomy and bilateral salpingo-oophorectomy for adenocarcinoma of the endometrium. Haemangiomata elsewhere in the genital organs have been reported (Schnedorf, 1941). Willis (1967) regards Fallopian tube haemangiomata as congenital malformations, but others describe them as true neoplasms (Ashley, 1978). Dilated cavernous blood vessels in the Fallopian tube can result from, torsion, trauma or inflammation (Ragins and Crane, 1947), but none of these factors were present in my patient or those reported by others with the possible exception of the patient described by Ebrahimi and Okagaki (1973). As with Patel *et al* (1972), my patient presented because of bleeding.

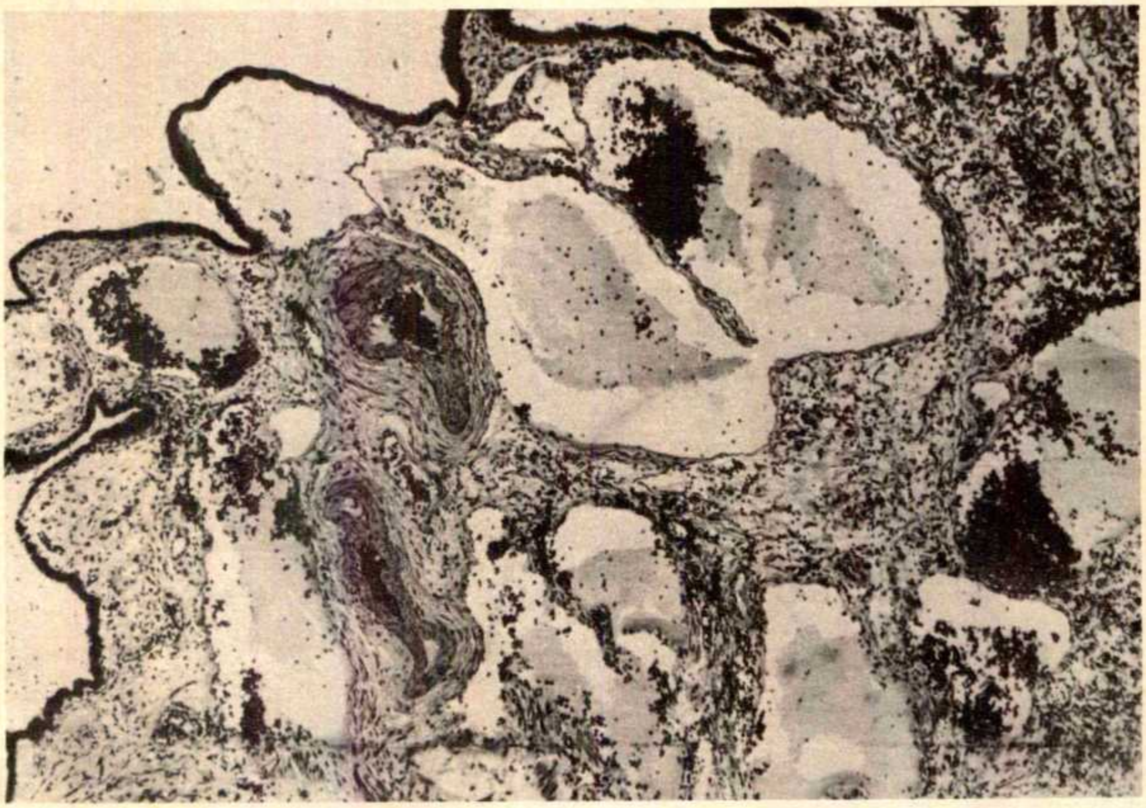

FIG. 2

Detail of haemangioma (haematoxylin and eosin ×63).

ACKNOWLEDGEMENT

I thank the Electron Microscopy Department for the photographic work, Professor J. R. Newton for permission to report this patient and the staff of the Morbid Anatomy Department for help and encouragement.

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A REPORT OF THE MEETING OF THE BLAIR BELL RESEARCH SOCIETY AT THE ROYAL COLLEGE OF OBSTETRICIANS AND GYNAECOLOGISTS ON 2nd APRIL, 1979

Four papers were presented to and discussed by the Society and afterwards the Duphar Lecture, 'Growing and Reproducing', was given by Professor Angus Thomson of Newcastle.

Prostaglandin Production by the Cervix (Observations in vitro *and* in vivo) was presented by Dr D. Ellwood on behalf of himself, Dr M. Mitchell, Dr Anne Anderson and Professor A. Turnbull from the Nuffield Department of Obstetrics at Oxford. Previous work on the ovine cervix with *in vitro* continuous superfusion had shown a specific increase in prostaglandin E (PGE) production. Work was extended to chronic catherisation of sheep to allow examination of PG production by the cervix in late pregnancy and partuition; these *in vivo* observations confirmed a rise in the PGE levels in the cervical venous effluent in parturition. The cervix was a potent intrauterine source of PGE, PGF and 13-14-dihydro 15-keto PGF. In the human, work has been done on specimens of cervix obtained at emergency Caesarean section or at first trimester termination hysterectomies. Perfusion experiments showed that the human cervix produced prostaglandins in pregnancy, PGE being quantitatively the most important. PGE seemed to be associated with the alterations of elasticity of the cervix while PGE and PGF caused contractions of the uterus. Ultrastructure examination showed that the collagen disolution of the cervix was not affected by either PGE or PGF but by arachidonic acid. There was no change in the collagen fibrils but the fibroblasts were more active. There was some discussion about whether prostaglandins were released after the trauma of late pregnancy and labour or were responsible for softening of the cervix. The latter was considered more likely because of the delay in labour produced by prostaglandin inhibitors.

The Use of Prostaglandin Pessaries in the Induction of Labour was presented by Dr J. M. Pearce on behalf of himself, Mr J. Shepherd and Mr C. Sims of Queen Charlotte's Hospital. They examined over 500 consecutive inductions of labour with 3 mg of prostaglandin E_2 vaginal pessaries. The population was divided into those with favourable and those with unfavourable cervical features. A lower proportion of the favourable patients required oxytocin augmentation of labour and there were no failed inductions and fewer Caesarean sections than with conventional induction with membrane rupture and intravenous oxytocin. No serious fetal or maternal side effects were reported in either group and the pessaries were easy to use on the labour wards. In discussion, the high induction rate (22 per cent) was commented upon. This obviously depends upon the population attending a given unit and it is difficult to compare rates from one centre to another. Comparisons were sought between patients treated by this method and those induced by more conventional oxytocic regimes.

Relationship between the Suckling-induced Prolactin Release and Lactogenesis was presented by Dr Howie on behalf of himself and Dr A. McNeilly from the Medical Research Council Unit of Reproductive Biology in Edinburgh. Lactating patients were examined in the first week of the puerperium, a cannula being placed in a forearm vein 30 minutes before breast feeding started. Serum prolactin measurements were then made before breast feeding and on eight occasions at set intervals for two hours after the start of feeding. There were very large variations of prolactin levels in both the basal measurements (0·3 to 7·0 units/litre) and in the response to suckling (0·1 to 10·7 units/litre); for individual women, the response was similar in consecutive feeds. A high correlation coefficient was found when relating prolactin levels at the initial feed to those at subsequent feeds. Mean basal levels of prolactin showed no significant change in the first week but the total amount of prolactin released rose up to Day 4 and fell after this. By test weighing babies, patients were divided arbitrarily into two groups—good feeders whose mean baby weight increased by 60 g or more at a feed and poor feeders. The mean prolactin response was not different between the two groups. Further, there was no correlation between test weights and prolactin response. A group of six patients whose babies were in the Special Care Nursery had lactation maintained with a breast pump. This, while providing a vacuum, did not stimulate the mother's nipple. In this group, the basal levels of prolactin on Day 6 were lower than the mean of those who were suckling their infants and receiving nipple stimulation, despite the good milk response of those using the breast pump. It would appear that whilst it is essential that the threshold value for prolactin is achieved to start lactation, there is no constant relation between success of breast feeding and serum prolactin levels.

The Influence of Intrauterine Undernutrition on Early Postnatal Growth in Light-for-dates Infants was presented by Dr D. Davies on behalf of himself, Dr P. Platts and Dr P. Wilkinson of Leicester Royal Infirmary Maternity Hospital. The aims of the study were (i) to describe the nutritional status at birth in terms of the Ponderal Index $\left(\frac{\text{weight (g)} \times 100}{\text{length}^3\text{ (cm)}}\right)$ of 47 light-for-dates babies; (ii) to see how intrauterine undernutrition influenced postnatal growth of weight, length and head circumference in the first six months after birth; and (iii) to define the period of 'catch up'. Twenty-four babies had a Ponderal Index below the third centile ('wasted'). Seven were between the third and tenth centile and 16 were greater than the tenth centile ('not-so-wasted'). Of these only one was above the 50th centile. 'Wasted' infants showed significantly higher rates of gain in weight, length and head circumference in the first month than the 'not-so-wasted' infants. Thereafter, growth rates of the two groups were similar. Compared with normal term babies, both 'wasted' and 'not-so-wasted' light-for-dates babies had higher rates of weight gain, length and head circumference growth over the first three months of life. These findings imply that (i) as a statistically defined group, light-for-date babies had experienced prenatal undernutrition; and (ii) the period of 'catch up' growth was the first three months after birth with the first month being particularly important for those 'wasted' babies.

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BOOK REVIEWS

Major Mental Handicap: Methods and Costs of Prevention. Ciba Foundation Symposium No. 59 (new series). Pp viii+226 with 34 figs and 43 tables. Elsevier/Excerpta Medica, Amsterdam, 1978. Price: US $23.00.

THE Ciba Foundation has again produced a superb volume on a topical subject of clinical, social and economic importance. The printed discussions which follow each paper ensure that the reader appreciates areas of controversy and lightens the serious nature of the subject by revealing the antics of a speaker who tries to wriggle out of answering a difficult question. Dr Hobel of California discussed his risk assessment system for identifying the high-risk pregnancy. The 'risk' approach has been used in his unit for the past ten years and he is carrying out prospective studies on intervention for specific indications. Hagberg showed that the incidence of cerebral palsy has fallen considerably in Sweden during the past 25 years but there has been no corresponding improvement in the incidence of children with mental retardation. A third of these children, both in Sweden and in this country, have Down's Syndrome and Eva Alberman pointed out that a programme of pre-natal diagnosis and termination of fetuses with Down's syndrome would have a considerable impact on the prevalence of severe subnormality. Dr Fitzhardinge discussed the disappointing results of the surviving infants of 1500 g or less treated in the intensive care unit of the Hospital for Sick Children in Toronto. Eighty-five per cent of those who survived an intracranial haemorrhage and 53 per cent of those who were small for gestational age had significant handicaps. Thirty per cent of infants weighing 1000 g or less had a significant handicap by 2 years of age. In contrast, at University College Hospital, the incidence of major handicap in infants of birth weight 1500 g or less was 10 per cent and the mean IQ was within the range expected for a normal population. Whether these differences were due to the reluctance of the Canadians to turn off the ventilator or the willingness of the obstetricians at U.C.H. to deliver tiny babies electively by Caesarean section was not clear. The possibility that the 65 referring hospitals had been starved of incentive and facilities by the known excellence of the Toronto unit was not explored. Dr Davies pointed out that at Hammersmith Hospital the incidence of major handicap among infants born weighing 1500 g or less had been constant at about 6 per cent over the previous 15 years but the proportion of apparently normal surviving children had increased. Dr Chapalain gave a paper on the French cost-benefit studies and there was a final discussion on research and U.K. priorities. Obstetricians who consider that a healthy baby is the object rather than a by-product of pregnancy will find that the Ciba Foundation has provided a volume which has combined essential information with entertainment.

H. B. Valman

Advances in Gynaecological Endocrinology—Proceedings of the Sixth Study Group of the Royal College of Obstetricians and Gynaecologists 1978. Edited by H. S. JACOBS. Pp i+410 with figures and tables. RCOG, London, 1978. Price: £5.00.

HAVING had the privilege of taking part in this study group, I am obliged to congratulate Dr Howard Jacobs on this volume, produced under his editorship and which reflects very accurately the substance and feeling of what was an important and stimulating meeting. The two principal topics—disorders of ovulation and hirsutism—were the subjects of papers by outstanding contributors and the discussions, here reported *in extenso* were not only an integral part of the meeting itself but undoubtedly add greatly to the value of this volume. A brief survey of the subjects and the principal contributors includes: the ovary and control of ovulation (Edwards), diagnostic tests (Shaw, Nillius), the defective luteal phase (Coutts) and its treatment (Macnaughton), the psychopathology (Crisp) and epidemiology and endocrinology (Nillius) of weight loss—related to amenorrhoea, ovulation induction therapy with LH-RH (Nillius), bromocriptine (Jacobs), clomiphene (Van Look) and gonadotrophins (Lunenfeld), pituitary tumours (Jenkins) and prolactin (Nabarro) in relation to amenorrhoea, prolactinomas and their management (Bessar), androgens in normal and virilized women (Horton), polycystic ovary syndrome (Baird), diagnosis of hirsutism (Barnes), hormones and the skin (Ebling), anti-androgens in general (Neumann) and cyproterone acetate in particular (Hammerstein). The most that the above list can do is whet the appetite of those interested to delve more deeply into this fascinating book. Their curiosity will be rewarded by a wealth of factual data and a great deal of wisdom.

Finally, the College is to be congratulated, not only for having organised the meeting itself but also on the remarkable achievement of having published its transactions within less than three months.

G. T. M. Swyer

Intrauterine Contraception, Volume 1, 1977. Edited by MAX ELSTEIN and RICHARD A. SPARKS. Pp i+81. Churchill Livingstone, Edinburgh, 1978. Price: £6.50.

THE purpose of this book is to review recent research in intrauterine contraception and it is one of a series entitled 'Annual Research Reviews' published in North America by Eden Press Inc. and in Britain by Churchill Livingstone. It is primarily designed to review the references cited in the Index Medicus during the twelve months from October 1976 to September 1977, though about 10 per cent of their references date from before 1976. The book therefore has no pretensions as a text book on all aspects of intrauterine contraception and refers the reader interested in the earlier background to a number of other standard works and reviews. Like its companion series 'Oral Contraceptives', by Michael and Maxine Briggs, the intention is to produce annually from now on, a similar review of each year's literature. Considering the constraints imposed by confining the review to one year of literature on the intrauterine contraceptive device (IUCD), this is a most competent review, readable and well-organised. The list of references alone would be of considerable value, both to research workers and clinicians. It is arranged in alphabetical order, includes full titles and first and last pages for each paper, and the names of all authors. The early chapters deal with clinical trials and animal studies on standard IUCDs and the newer designs, and the two-way interaction between IUCDs and the uterine environment. There are separate chapters on hormone-releasing IUCDs, the lost IUCD, pelvic infection, pregnancy and menorrhagia as they relate to the IUCD, and on intratubal devices. The final chapter reviews articles on the place of the IUCD in contraceptive practice. By definition, a review of this kind should be impartial, but this inevitably means that the reader feels at times a lack of guidance from the editors, in the evaluation of conflicting findings and conflicting advice from different authorities in the literature. This was noticeable for example in Chapter 5, which reviews findings relevant to clinical practice concerning duration of use of copper devices. However, in general, the editors have been successful in assisting the reader to evaluate the relative importance of different studies, chiefly by devoting more space to those which were the better designed and executed. They have also achieved commendable brevity. This and its companion volumes can be warmly recommended for clinicians who wish to ensure that their family planning practice reflects the latest research findings, and for research workers. The book is a good bird's eye view of one year's literature, and also helps the reader to decide which particular publications should be sought out for more detailed study.

J. Guillebaud

Colposcopy. A Scientific and Practical Approach to the Cervix and Vagina in Health and Disease. Second Edition. Edited by M. COPPLESON, E. PIXLEY and B. REID. Pp vii+492 with 305 figs and tables. Charles C. Thomas, Illinois, 1979. Price: $36.50.

OVER the past few years interest in colposcopy has been increasing, both in the United Kingdom and in other English speaking countries where its use has not hitherto being widespread. A corresponding trickle of books has been appearing, both instructive texts and atlases, most of which are of high quality. The first edition of the book by Coppleson, Pixley and Reid was one of the earliest textbooks in colposcopy in English and set the standard by which the others were necessarily judged. A second edition has now been produced and, although the general layout is the same as in the first edition, there have been a number of additions and improvements, reflecting both advances in knowledge and changes in presentation which are the result of many years of experience by the authors in colposcopy teaching courses. There are sixteen chapters divided into seven sections. In addition to the introduction, these sections cover the scientific basis of colposcopy, the technique of colposcopy, colposcopic morphology, recent advances, difficulties of colposcopic interpretation and the practical uses of colposcopy. Although this layout is logical, there is a great deal of repetition, particularly in the sections on the scientific basis and colposcopic morphology. This in itself is, of course, no bad thing in a volume which is designed for teaching, but it does mean jumping from section to section to look for details of a particular subject. The text is well written and easy to read and understand and the illustrations, which, with one exception, are in black and white, are generally good. However, there are one or two which look as if they have been sent from Sydney by satellite. The additional material is on vaginal adenosis and changes induced by DES exposure *in utero*, with the chapters contributed respectively by Stafl and Townsend. These are problems which are more often seen in the United States but nevertheless we should be aware of them elsewhere. It is refreshing to see the slight mellowing which has taken place since the first edition; a paragraph is included which deals with the major discrepancies which may be found between the colposcopic and histological diagnoses, even though elsewhere in the book it is implied that the colposcopic appearances may give a more accurate assessment of the biological behaviour of the epithelium than histology in some instances where a discrepancy is found. The last two chapters are particularly valuable. One deals with conditions which may cause colposcopic abnormalities but which have a minor or insignificant underlying pathology and the other describes in detail the ways in which the colposcopic examination helps in the management of the patient in the whole range of situations in which it is used. This is a highly authoritative text from one of the world's leading colposcopist and it merits a place in the bookshelf of every practicing colposcopists. It could also be read with profit by pathologists who are required to interpret colposcopic biopsies.

M. C. Anderson

Notebook of Medical Physiology: Endocrinology. By Ross W. Hawker. Pp 189 with illustrations. Churchill Livingstone, Edinburgh, 1978. Price: £2.95.

Introduced as a revision text for postgraduate students studying for the primary examination of all the Royal Colleges, this book is well worth reading. In addition to a section on general medical endocrine physiology it has a very useful section devoted to maternal, fetal, perinatal and neonatal physiology. The information is presented as a series of facts illustrated by useful flow diagrams, but necessitates reference to more conventional texts for resolution of any points which require amplification. Unfortunately the self assessment material is not in keeping with the standard set by the rest of the book in that not all the M.C.Q. fulfill the requirement of being both unambiguous and having a definite answer.

G. M. Masson

Early Developmental Hazards: Predictors and Precautions. Edited by F. D. Horowitz. Pp xvi+114 with 12 tables. Westview Press Inc, Boulder (Colorado), 1978. Price: £9.15.

This slim volume is the 17th in the American Association for the Advancement of Science symposia series. It contains five papers that were presented at a symposium held in Denver in 1977 by well known behavioural and developmental psychologists. In the first chapter Dr Horowitz discusses some of the issues concerning developmental hazards confronting young infants. Papers by Dr Sameroff and Dr Leiderman consider environmental factors influencing infant development and social bonding. Dr Lipsitt examines data from modern studies on the sudden infant death syndrome, while Dr Trygg Engen reviews research on the conditions that influence children to ingest harmful substances. In the epilogue, the editor, Dr Horowitz, considers various environmental and biological factors affecting the development of the infant and young child. While this is an interesting little book and includes a useful list of 147 references, it is exceptionally expensive for what it contains.

P. M. Dunn

Corscaden's Gynecologic Cancer—Fifth Edition. By S. B. Gusberg and H. C. Frick. Pp vii+494 with illustrations. Williams & Wilkins, Baltimore, 1978. Price: $49.50.

The scope of this well-illustrated standard work from New York has been widely and wisely enlarged. There are added chapters on principles of radiotherapy and of chemotherapy as well as on endocrinological aspects of gynaecological cancers. Particularly welcome is a section on the causes and treatments of pain in these malignancies. A new chapter on basic and clinical immunology for the gynaecologist has a glossary of immunological terms appended. The retention of a chapter on the menopause is relevant where that condition results from therapy, but the discussion extends from the specific to the general, though the supplementation of oestrogen by progestogen in treatment is not mentioned. The conclusion to this chapter commences: "The era of general gynecologic support for the administration of prophylactic estrogen to all postmenopausal women is over. This practice has been abandoned by all but a brave minority of endocrinologists with a zealous interest in mythology". These statements will raise some hackles! This edition bears witness to advances made in this decade and to the necessity to include epidemiology and biostatistics when considering the problems of gynaecological cancers. It is therefore somewhat depressing to find the following sentence repeated unaltered from the 1970 edition: "Simply by applying the knowledge which is now available, so that both the patient and physician may do their part, we can raise the 5-year survival from about 40 per cent to approximately 80 per cent among those patients afflicted with gynecologic cancer".

S. Bender

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CORRESPONDENCE

Melatonin in the Maternal and Umbilical Circulations during Human Parturition. Mitchell, M. D., Bibby, J. G., Sayers, L., Anderson, A. B. M., and Turnbull, A. C. (1979): *British Journal of Obstetrics and Gynaecology*, **86**, 29.

From: A. N. W. Evans and J. A. Smith.

Sir,

We would like to comment on the paper by Mitchell *et al* (January, 1979) describing plasma melatonin levels found in pregnant and labouring women, and in their babies at birth.

Investigations in a variety of animals have demonstrated that serum melatonin levels usually show a circadian rhythm related to the day-night cycle with a nocturnal peak and a diurnal trough. A prominent circadian rhythm has been demonstrated in the blood (Smith *et al*, 1977) and urine (Lynch *et al*, 1975) of human adults, which is resistant to short term disruption of the light-dark cycle (Jimerson *et al*, 1977) although inter-individual differences are great.

A circadian rhythm of plasma melatonin has been described in pregnant women (Matthews *et al*, 1977). We have measured cord blood melatonin (Evans *et al*, 1979) in mixed arterial and venous cord blood samples, and showed a circadian rhythm of melatonin levels, low by day and high by night.

We therefore feel that it is essential to state accurately the time at which blood is sampled for melatonin.

Mitchell *et al* only stated that samples were taken between 0900 and 2230, and it is therefore not surprising that their mean values fall between the trough and peak values reported by Matthews *et al* (1979).

Yours, etc,

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Birth Weight: Analysis of Variance and the Linear Additive Model. Keeping, J. D., Chang, A., Morrison, J., and Esler, E. J. (1979): *British Journal of Obstetrics and Gynaecology*, **86**, 437.

From: D. G. Altman and E. C. Coles.

Sir,

We like the idea of calculating expected birth weight by allowing for the effects of a set of relevant factors, and at first sight the paper by Keeping *et al* (June, 1979) achieves this. However, we fear that the analysis which they carried out was incorrect, so that their results are substantially misleading. We say this for two reasons.

(1) We are concerned that their presumption of lack of interaction in the data may not be justified. We would be very surprised if, for example, parity was not strongly correlated with maternal age, or if height was not correlated either with parity or with patient status (public or private). To presume that there are no interactions because of difficulty in testing them is unacceptable. In any case, the authors have tested interactions with gestational age (although they report that none was statistically significant), so they could surely have studied the other two-way interactions. This can be done very simply by adding the interactions one at a time to the model. Without such an investigation of interaction it is impossible to accept that the model proposed is an appropriate or even a useful one. If interactions really are present, then the 'loading

weights' for one factor will depend upon the patient's category in some other factor, and the loading weights which they have given will be misleading. For example, if maternal age and parity are related it would not be possible to give a single set of loading weights for each of these factors.

(2) The only correct way of obtaining the desired linear additive model is by multiple regression. There are, however, two reasons for doubting whether this is the procedure that was used.

Firstly, the authors make no mention of regression in the paper, and their reference to a statistical textbook is to a chapter which deals solely with the analysis of variance of balanced data (that is, data with the same number of cases for every combination of categories). Secondly, the loading weights for gestational age can be derived straight from the raw data for the total sample by subtracting 3406 g from the respective means (this figure being the mean birth weight of all 14 046 babies delivered between 36 and 42 weeks). Since it is inconceivable that the results from the analysis of 9262 births could agree exactly with the raw data for the 14 046 births (whatever analysis was performed) we must conclude that the loading weights for gestation were not derived from the model but from the raw data.

If the loading weights for all the other factors were derived in this way, they are not independent of each other. This means that they should not be added together in the way suggested to obtain an adjusted expected mean birth weight (or centile), and that the loading weights do not reflect the importance of each factor independently of the others. Incidentally, the relative importance of a factor should be judged by the amount of variation explained, not by the range of the loading weights (which will depend in part on the number of categories).

The points which we have raised are not statistical niceties, they are fundamental and have major practical implications. Without an analysis of at least the obvious interactions and a clear description of the exact methods used, we could not recommend others to make use of the findings reported, or to use similar methods on their own data.

Yours, etc,

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CORRESPONDENCE

Unstressed Antepartum Cardiotocography in the Management of the Fetus Suspected of Growth Retardation. Flynn, A. M., Kelly, J., and O'Conor, M. (1979): *British Journal of Obstetrics and Gynaecology*, **86,** 106.

From: L. M. Hill.

Sir,

In their article, the authors divide the non-stress test into two groups: reactive and non-reactive. The non-reactive test is further subdivided in order of severity as suspect, flat and ominous.

The 'suspect' group appears to only have a decrease in baseline variability; an evaluation that is often difficult to make with an external monitoring system. A 'flat' tracing would be characterized as non-reactive in the United States and followed by a contraction stress test to further evaluate fetal states. I would submit that an 'ominous' tracing is merely a spontaneously positive contraction stress test, a group with a much higher perinatal mortality if further evaluation (amniocentesis, real-time ultrasound assessment of fetal biophysical parameters) and possible intervention is not undertaken (Martin and Schifrin, 1977).

The above points in no way detract from the authors' contribution; I merely wished to clarify their results with respect to current terminology in this country.

Yours, etc,

Lyndon M. Hill
Department of Obstetrics and Gynecology
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Minnesota 55901

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Martin, C. B., and Schifrin, B. S. (1977): *Perinatal Intensive Care.* Edited by S. Aladjem and A. K. Brown. St Louis, Missouri, C. V. Mosby Co, p 155.

the oral pregnancy test which have rather tardily exonerated the work of Gal *et al* (1967). A similar effect of hormone support therapy (giving a risk ratio as high as 1·7:1, though on small numbers) is perhaps underplayed in a potentially misleading statement that suggestions of risk "have not been confirmed." Perhaps not, but they have been strengthened. A similarly curious use of language occurs also in the discussion of benzodiazepine, one of the many drugs studied in the project described by these authors. Perhaps the most valuable chapter of all is that by Brent. He gives a masterly review of the risks from ionising radiation to the fetus, the best available anywhere. He has plausible explanations for the differences between man and most experimental mammals in radiosensitivity of the central nervous system and in the radio-inducibility of structural malformations elsewhere. The confused data on pre-natally induced leukaemia are carefully reviewed and improved guidance emerges concerning the taking of X-rays during pregnancy, the 10-day rule being consigned to oblivion. Despite one or two less interesting chapters that cover mainly old ground, this book is an invaluable addition to the teratological literature.

J. Renwick

before tackling a difficult case or problem, and yet there is a chapter on epidural and caudal anaesthesia and another on resuscitation of the neonate which are not really fulfilling this role. It is surprising to find whole chapters devoted to paracervical block and the oxytocin challenge test, and yet there is no mention of the use of prostaglandins either for cervical ripening, induction of labour or termination of pregnancy. Many obstetric departments keep some form of manual to guide junior staff, and maintain uniformity of practice both in the antenatal ward and the labour ward. Such guides are essentially local, taking into account the facilities, staffing and geography of a particular department. Although some of the chapters in this book contain useful schemes of management, I do not think sufficient of it would be applicable to the practice of other hospital to make it a really useful addition to the Ward Library or Resident's On-Call room.

M. Setchell

Practical Obstetric Problems—Fifth Edition. Edited by Ian Donald. Pp vii+1071 with illustrations. Lloyd-Luke, London, 1979. Price: £15.00.

The fifth edition of Professor Ian Donald's famous text book will be welcomed by practising obstetricians everywhere. But their welcome will be tinged with considerable sadness for Professor Donald describes it as his last obstetrical will and testament. Few bequeath so much in their will as he has and this edition will gain him further admirers for it is very much up to his very high standard. Apart from revision of much of the text to bring it up to date in relation to the ever changing practices of our time, there have been specific new sections added. Notable ones are the genetics of fetal abnormality by Professor Malcolm Fergusson-Smith and the biochemistry of obstetrics by Dr Robert Logan. Professor Donald himself has thoroughly revised the section on ultrasound and has included some of the modern technical advances such as grey-scaling and real-time scanning. There are few criticisms to be made. Perhaps the new section on the genetics of fetal abnormality might have said a little more on the subject of antenatal diagnosis of haemoglobinopathies and your reviewer is sorry to see the alleged Dystocia dystrophia syndrome rearing its ugly (very ugly) head again. These are minor points, however. The broad canvas of the book will remain, as its predecessors have done, as a splendid testament to a famous obstetrician and a fine man.

Sir John Dewhurst

A User's Guide to Diagnostic Ultrasound. By I. M. Shirley, R. J. Blackwell, G. Cusick, D. J. Farman and F. R. Vicary. Pp v+329 with illustrations. Pitman Medical, Kent, 1978. Price: £12.00.

This book departs from the usual format in that it is in two distinct sections. The first half deals with the basic principles and theoretical aspects of ultrasound as well as the various types of diagnostic machines. Most books on this subject are a great deal less easy to read and understand than this text and the authors are to be commended on this achievement. The clinical section deals exclusively with abdominal scanning and in this the title may be regarded as a little misleading. Nevertheless, the section is comprehensive enough and throughout the authors point out potential difficulties and suggest methods of overcoming them. These tips are most helpful and will doubtless be of considerable use to virtually everyone involved in providing an ultrasonic service. Some of the pictures are of a poorer quality than can be obtained with some of today's machines but in general the illustrations make their points well. Although this book cannot be regarded as a reference book, it is one which this reviewer would recommend to almost every clinical ultrasound department. The price of £12.00 is very modest by current standards and for this the publishers deserve a word of praise.

M. J. Bennett

Contributions to Epidemiology and Biostatistics. Vol. 1. Epidemiologic Methods for Detection of Teratogens. Edited by M. A. Klingberg and J. A. C. Weatherall. Pp x+198 with 22 figs and 16 tables. S. Karger, Switzerland, 1979. Price: $49.75.

Much of this excellent volume (the first of a set of six) is important to obstetricians. There is a good chapter by Nishimura emphasising that the testimony of experimental animals is still inadequate for the human situation. For example, they respond entirely differently from man to the polychlorinated biphenyls that produced human coca-cola babies in Japan in 1968. A chapter by Leck gives a penetrating numerical analysis of the risks from certain drugs during pregnancy; another one, by Bakketeig, bewails the failure of surveyance programmes to indicate what mechanisms underlie increased malformation rates, such as that of hypospadias in Scandinavia from 1972; and yet another good chapter, by an Atlanta group, concerns occupational hazards that affect fetuses, particularly those of nurses. An article by Weatherall and Greenberg presents their new data on the teratological effect of

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BOOK REVIEWS

Pathology of the Female Genital Tract. Edited by ANCEL BLAUSTEIN. Pp xx+897 with 1245 figs and tables. Springer-Verlag, New York, 1977. Price: $52.00.

THIS weighty tome is the combined work of 28 authors because, as the Editor states in his preface, "the expansion of information in the field of gynecologic pathology renders single authorship obsolete." After reading the book, I wonder if there is even a place for a single-volume work on gynaecological and obstetrical pathology now. Each subject within the sub-specialty has enlarged to such an extent that full coverage would result in a book of even greater size. Very good monographs are now available in most fields of gynaecological pathology and it is to these that the reader will turn for detailed information. Setting aside the question of the need for a book such as this, how far has the editor achieved what he set out to do? Twenty-six chapters cover the pathology of the female genital tract, from the vulva to ovary, with reference to normal histology, anatomy and physiology in most, but not all, sections. Five chapters deal with implantation, placental pathology, trophoblastic disease and abortion. The cytology of the female genital tract is covered in one chapter and a further chapter gives suggestions regarding the gross description and processing of material received by the pathologist. There is an introductory chapter on the embryology and congenital malformations of the female genital tract, a chapter on disorders of female sex differentiation, one on the pathological factors involved in infertility and two concluding chapters, one on animal models for tumours of the ovary and uterus and the other on spontaneous tumours of the uterus and ovaries in animals. As is inevitable with multi-author books, some chapters are better than others; particularly worthy of comment are the excellent chapters on the cervix and those on sex-cord stromal tumours and germ cell tumours of the ovary. However, it seems a mistake to attempt to cover the whole of the cytology of the female genital tract in a mere 26 pages; a subject dealt with as briefly as this can be of little value to anyone but a beginner. The cytology chapter also illustrates another problem in the multi-author book, which is inconsistency in terminology. In his discussion on the histology of cervical intraepithelial neoplasia, Alex Ferenczy strongly advocates Richart's CIN nomenclature and yet the dysplasia/carcinoma *in situ* terminology is used alone in the chapter on cytology. This inconsistency is seen again in the chapter on ovarian neoplasms in childhood and adolescence. Not only is most of this chapter largely repetition of what has been discussed in the previous three chapters, but a different terminology has been adopted. On the whole, the text is written in an easily understood style but some carelessness is evident: 'Ascherman' and 'Asherman' appear in the same paragraph, as do 'mucus' and 'mucous,' both as nouns. Most of the illustrations are good and there are many transmission and scanning electron micrographs. Some of the photographs seem to be too big, so that the book has to be held at arm's length for the whole illustration to be taken in, and a few are spoilt by being out of focus or having uneven illumination. The bibliography is comprehensive and up-to-date. The editor has achieved his aims, albeit somewhat unevenly. Despite the above criticisms, this book is probably the best single volume on gynaecological and obstetric pathology available and it will no doubt find a useful place in general histopathology departments. However, for specialist departments, it must be considered a compromise.

M. C. Anderson

Practical Obstetrics and Gynecology—Manual of Selected Procedures and Treatments. By V. INSLER and R. HOMBURG. Pp viii+112 with 43 figs and 7 tables, loose-leaf binding with thumb index. S. Karger, Switzerland, 1979. Price: $49.25, DM 95.

THIS loose-leaf volume attempts to lay out standardised schemes of management for some 32 gynaecological and obstetric problems and procedures. It is written by two obstetricians from the 'Zahalon' Hospital in Jaffa (Israel), and the style of writing is a curious mixture of American folksiness and heavy technical jargon. Many chapters contain flow diagrams to illustrate the scheme of management, but some of these are so complex that they seem to complicate rather than simplify management; for example one in the section on management of post-date pregnancy contains 17 'boxes.' The preface states that the book is a 'Service Manual,' which may be consulted for 10 minutes hyperprolactinaemia with or without pituitary tumour, treatment with lisuride at a dose ranging from 50 to 200 μg daily lowered serum PRL levels in nine out of eleven subjects; these nine patients resumed menstrual cycles and all but one ovulated (De Cecco *et al*, 1978).

In rodents, lisuride has dopaminergic and antiserotoninergic activities (Horowski and Wachtel, 1976). In acromegalic patients, pretreatment with pimozide, a potent dopamine antagonist, reduces the PRL and GH suppressive action of lisuride (Liuzzi *et al*, 1978). It would thus appear that lisuride lowers the serum PRL levels in humans by its dopaminergic action. Dopaminergic drugs may act directly on the anterior pituitary and lisuride even acts on the pituitary transplanted to the renal capsules of the hypophysectomized rat (Gräf *et al*, 1977).

ACKNOWLEDGEMENTS

Lisuride was kindly supplied by Schering AG Berlin/Bergkamen. This study was supported by Consiglio Mazionale delle Ricerche, Rome (Special Project on Reproductive Biology).

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samples were assayed in triplicate. Statistical analysis was performed by a Student's t test.

RESULTS

Lisuride effectively prevented lactation in all patients (Table I). Half of the 26 patients treated with 300 μg of lisuride daily and one-third of the 27 patients treated with 600 μg of lisuride daily had rebound lactation. With the single exception of one patient with the lower dose of lisuride, all rebound lactation was controlled by administration of 600 μg of lisuride daily for a further week.

Serum PRL levels fell rapidly in both groups during treatment (Fig. 2) and the mean basal PRL levels were not significantly different in the two dosage groups but the differences in mean serum PRL levels between the two groups were significant on days 5 and 7 ($p < 0{\cdot}01$). The differences in PRL concentration between the lactating controls and treated subjects were significant ($p < 0{\cdot}01$) from the third day onwards.

There were no untoward side effects and no significant changes in pulse rate, blood pressure, hepatic and renal function tests and full blood counts.

DISCUSSION

Lisuride was effective in inhibiting lactation and lowered puerperal serum PRL levels in a dose-dependent manner; 600 μg daily reduced serum PRL to concentrations found during the normal menstrual cycles within seven days. These results are similar to those of Utian *et al* (1975) who used 5 mg of bromocriptine daily.

Rebound lactation occurred slightly less frequently with the 600 μg tablets of lisuride than with bromocriptine given for seven days at doses ranging from 2·5 to 7·5 mg daily (Rolland and Schellekens, 1973).

In patients with secondary amenorrhoea and

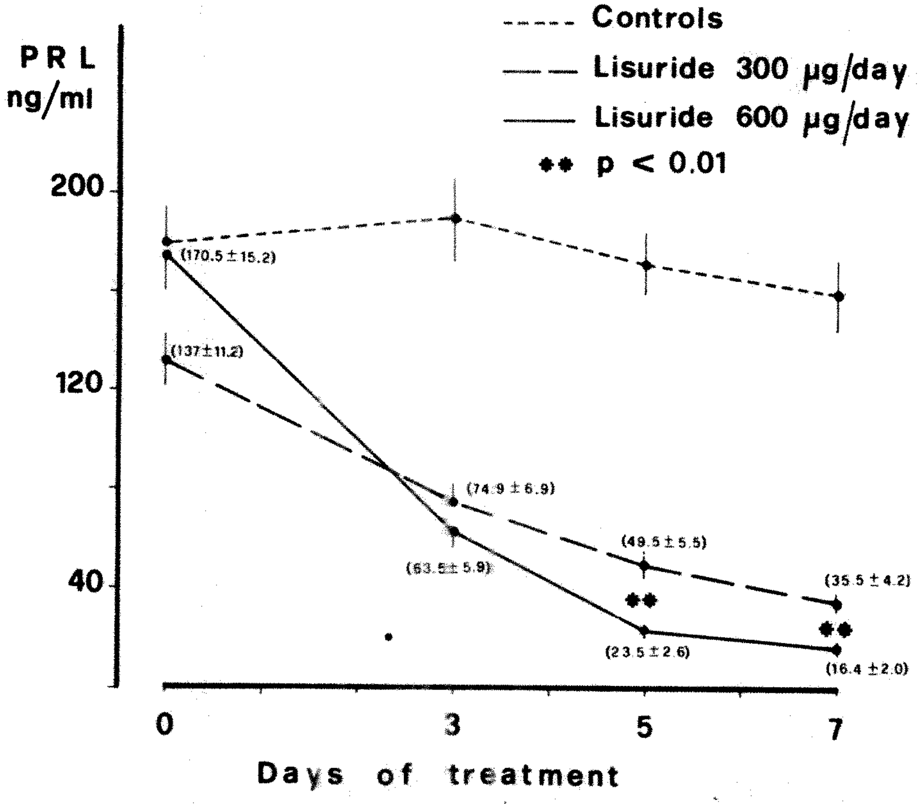

FIG. 2

Serum prolactin levels (Mean ± SE) in eight lactating women (controls) and in the two groups of treated patients.

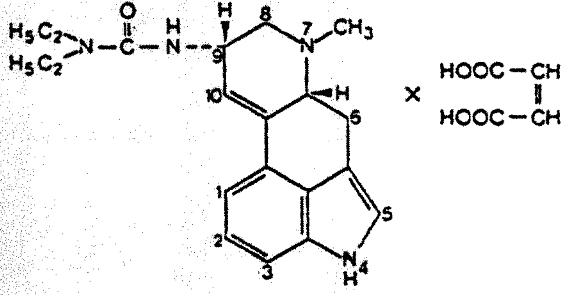

FIG. 1

Chemical structure of lisuride hydrogen maleate

groups showed no significant differences in weight, age, parity and gestational age at delivery.

Milk secretion, congestion and breast pain were assessed twice a day. Blood pressure, pulse rate and urine output were recorded daily. Before and after treatment, hepatic and renal function tests and a full blood count were done, and blood samples for PRL assays were obtained from all the patients at 0800 hours before the first dose of lisuride and on days 3, 5 and 7 of the puerperium.

Eight lactating women served as controls; blood samples were taken from these patients on the same days but at two or more hours after breast feeding.

Serum PRL was measured by a specific homologous radioimmunoassay (Sinha *et al*, 1973) using kits from Biodata (Rome). One ng of standard was equivalent to 1 ng of NIH prolactin F.1 standard. The limit of sensitivity was 0·6 ng/ml; intra- and interassay coefficients of variations were 4·6 and 10·2 per cent respectively. Our values for normal non-pregnant women range from 5 to 20 ng/ml. All

TABLE I

Effect of treatment with lisuride in 53 puerperial patients

		Congestion		Milk production		Breast pain	
		Dose of lisuride (μg/day)		Dose of lisuride (μg/day)		Dose of lisuride (μg/day)	
Day of treatment	Score	300	600	300	600	300	600
1	good	24	27	26	27	26	27
	fair	2	0	0	0	0	0
	poor	0	0	0	0	0	0
2	good	23	26	25	27	25	27
	fair	2	1	1	0	1	1
	poor	1	0	0	0	0	0
3	good	21	25	22	25	24	26
	fair	2	1	2	1	1	0
	poor	3	1	2	1	1	1
4	good	20	26	21	26	26	27
	fair	3	1	3	1	0	0
	poor	3	0	2	0	0	0
5	good	25	26	25	26	26	27
	fair	1	1	1	1	0	0
	poor	0	0	0	0	0	0
6	good	26	27	26	27	26	27
	fair	0	0	0	0	0	0
	poor	0	0	0	0	0	0
7	good	26	27	26	27	26	27
	fair	0	0	0	0	0	0
	poor	0	0	0	0	0	0

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EFFECT OF LISURIDE ON INHIBITION OF LACTATION AND SERUM PROLACTIN

BY

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Summary

Lisuride, a new semisynthetic ergot derivative, was given to 53 women to inhibit lactation; 26 women had 300 μg daily and 27 had 600 μg daily for seven days. Eight lactating women acted as controls. Lisuride effectively inhibited lactation and also suppressed the serum prolactin levels; the latter effect was dose related. Lisuride produced no untoward side effects.

BROMOCRIPTINE, a dopaminergic drug, can inhibit lactation (Varga *et al*, 1972; Del Pozo *et al*, 1972; Rolland and Schellekens, 1973) and so can methergoline, an antiserotoninergic drug (Delitala *et al*, 1977). Lisuride (Fig. 1) is a new semisynthetic ergot derivative with dopaminergic activity (Horowski and Wachtel, 1976; Gräf *et al*, 1976) and antiserotoninergic activity (Benkert and Eversmann, 1972) in rodents. Lisuride also reduces TRH- and sulpiride-induced hyperprolactinaemia in healthy women (Horowski *et al*, 1977) and significantly reduces plasma prolactin (PRL) concentrations in patients with pituitary tumours or functional hyperprolactinaemia (Liuzzi *et al*, 1978; De Cecco *et al*, 1978).

The aim of our study was to evaluate the effect of lisuride on lactation and post-partum serum PRL levels.

METHODS

Fifty-three women who did not wish to breast feed were studied. All gave informed consent. All patients had delivered vaginally and none had been given general anaesthesia, corticosteroids, diuretics or phenothiazines.

Treatment was started within 24 hours of delivery. The lisuride tablets were given three times a day (0800, 1500 and 2300 hours) for seven days. The first group of 26 patients received 100 μg lisuride tablets and the second group of 27 patients 200 μg tablets. The two

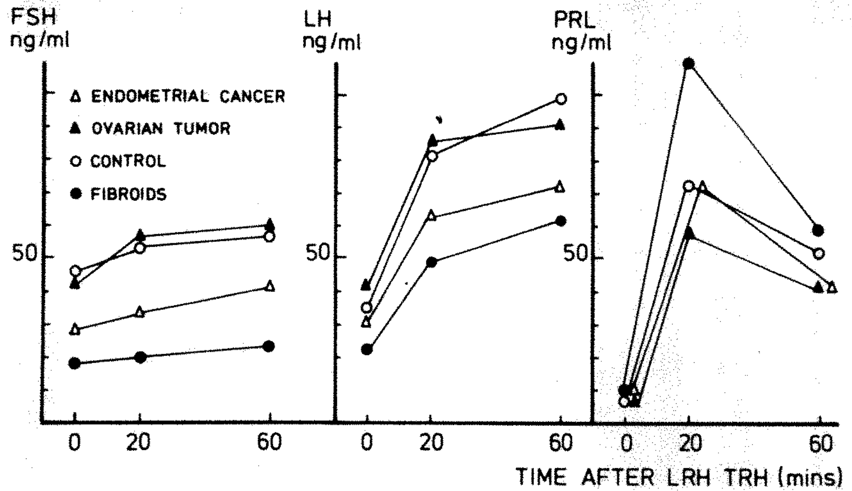

FIG. 4

Mean levels of FSH, LH and prolactin before and after stimulation with GnRH-TRH in patients with endometrial cancer, fibroids or ovarian tumour and in controls.

normal oestrogen level in women with fibroids since oestrogens exert a negative feed-back effect on FSH secretion but a stimulating effect on PRL. It is known, however, that women with fibroids have normal oestradiol levels (Spellacy *et al*, 1972). It would thus appear that pituitary function may be abnormal in patients with uterine fibroids. Changes in pituitary function have also been observed during hypoglycaemic pituitary stimulation when the level of growth hormone is twice as high in women with uterine fibroids than in controls (Spellacy *et al*, 1972). It is not known at present whether these results indicate an association, or are cause and effect. Since PRL can be implicated in the development of breast cancer in humans (Boot, 1970; Ohgo *et al*, 1976) and promotes the growth of cancer of the uterine cervix in mice (Forsberg and Breistein, 1976), it is possible that PRL could also be related to the growth of the fibroids.

It has been reported that the excretion of immunologically active LH was higher in patients with endometrial cancer than in controls while the biological LH activity did not differ (Dilman *et al*, 1973). In contrast, Brown (1974) found that LH secretion was diminished in the presence of endometrial carcinoma. Benjamin (1974) observed that the growth hormone level and its response to hypoclycaemia was higher in women with endometrial cancer than in the age-matched controls. We can add that the levels of FSH, LH and PRL and their responses to GnRH–TRH stimulation were normal in women with endometrial cancer and in those with ovarian tumours. It thus appears unlikely that pituitary dysfunction is responsible for the development of these tumours.

ACKNOWLEDGEMENT

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TABLE II

Basal levels and maximal increments of FSH, LH and prolactin during GnRH-TRH stimulation tests in patients with endometrial cancer, fibroids or ovarian tumour

	Basal level (ng/ml) Mean ± SD			Maximal increment (ng/ml) Mean ± SD		
Diagnosis	FSH	LH	PRL	FSH	LH	PRL
Endometrial cancer	29·3±23·0	30·3±42·1	6·1±4·2	10·7 ±7·1	46·9±37·4	66·7 ±21·5
Fibroids	17·1±16·2**	22·3±16·5	9·3±8·1	5·8* ±4·2	44·4±24·4	103·2** ±45·2
Ovarian tumour	46·5±22·4	42·7±21·8	6·6±4·6	14·6 ±12·4	62·7±32·9	49·5 ±28·6
Controls	46·6±22·7	35·0±17·6	6·4±2·7	11·0 ± 9·8	57·5±35·8	65·5 ±19·8

* $p < 0{\cdot}05$ ** $p < 0{\cdot}01$—statistical significance in comparison with the control group.

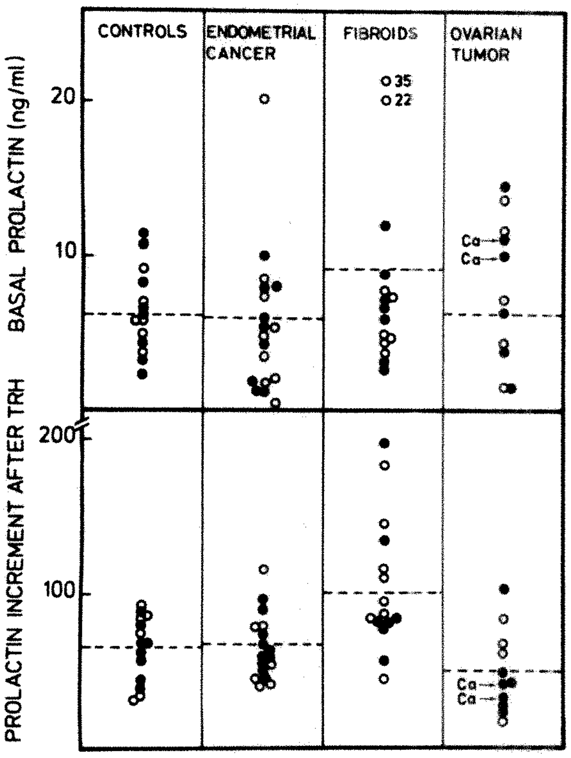

FIG. 3

Baseline level of prolactin and maximal increment following TRH administration in patients with endometrial cancer, fibroids or ovarian tumour and in controls. Ca = cancer, ○ = premenopausal, ● = postmenopausal. The dotted line indicates the mean hormone level.

in the controls (Table II). The mean of the maximal FSH increase following GnRH administration was normal in women with endometrial cancer or with ovarian tumour but significantly ($p<0{\cdot}05$) reduced in patients with fibroids (Fig. 1, Table II).

The basal LH level as well as the LH responses to GnRH were similar in all patient groups (Fig. 2, Table II).

Two patients with fibroids had higher than normal PRL concentrations (22·3 and 35·0 ng/ml, respectively), but the mean basal PRL level did not differ significantly between the groups (Fig. 3, Table II). Each woman responded with a marked serum PRL elevation to TRH administration (Fig. 3). The mean PRL increment of 103·2±45·2 in women with fibroids was greater ($p<0{\cdot}01$) than that of 65·5±19·8 ng/ml found in the controls.

The gonadotrophin levels increased throughout the stimulation test while PRL reached its maximum at 20 minutes (Fig. 4). There was no difference between patients with malignant or benign tumours in this respect.

DISCUSSION

We have studied pituitary function by GnRH–TRH stimulation tests in patients with endometrial tumour, fibroids or ovarian neoplasms and in age-matched controls.

Apart from the conspicuous individual variation in FSH, LH and PRL levels, the patients with fibroids differed significantly from the controls. They had a low FSH level and a diminished FSH response to GnRH. In addition, the PRL response to TRH was excessive. These findings could be explained by a higher than

TABLE I

Age and menstrual status of patients studied

Diagnosis	No. of women	Age (years)		Premenopausal	Postmenopausal*
		Mean	Range		
Endometrial cancer	17	53·5	47–56	8	9
Fibroids	15	52·3	46–55	8	7
Ovarian tumour	11	54·4	49–58	5	6
Controls	14	54·2	48–56	6	8

* Amenorrhoea of over six months duration.

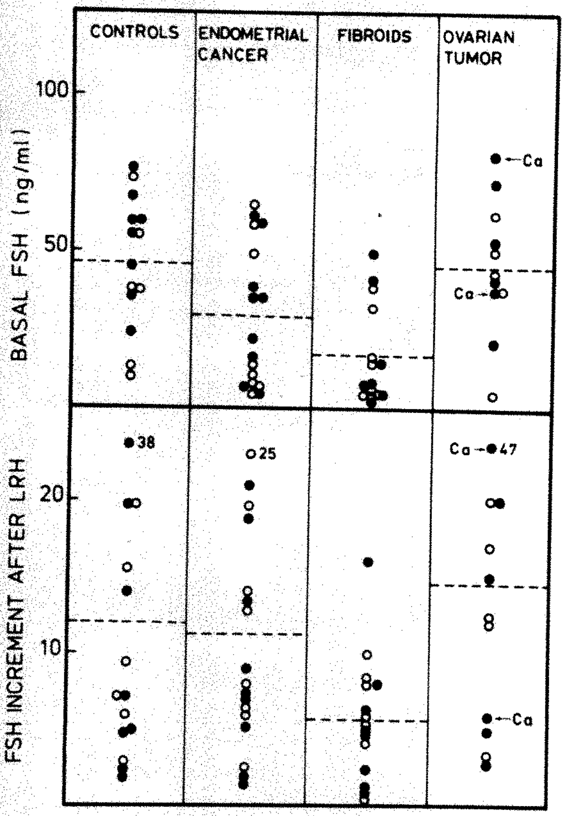

FIG. 1
Baseline level of FSH and maximal increment following GnRH administration in patients with endometrial cancer, fibroids or ovarian tumour and in controls. Ca = cancer, ○ = premenopausal, ● = postmenopausal. The dotted line indicates the mean hormonal level.

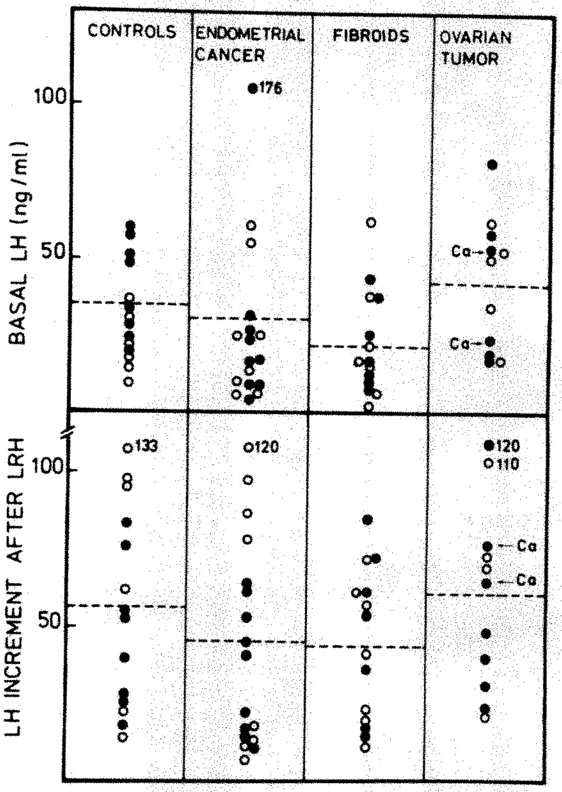

FIG. 2
Baseline level of LH and maximal increment following GnRH administration in patients with endometrial cancer, fibroids or ovarian tumour and in controls. Ca = cancer, ○ = premenopausal, ● = postmenopausal. The dotted line indicates the mean hormone level.

luteinizing hormone (LH) and prolactin (PRL) levels were measured by radioimmunoassays (Hammond *et al*, 1977). Student's t-test was employed for statistical analysis of the results.

RESULTS

Although the FSH range was fairly similar in all patient groups (Fig. 1), the mean serum FSH level in women with fibroids was lower than that

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PITUITARY GONADOTROPHINS AND PROLACTIN IN PATIENTS WITH ENDOMETRIAL CANCER, FIBROIDS OR OVARIAN TUMOURS

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Summary

The serum levels of follicle stimulating hormone (FSH), luteinizing hormone (LH) and, prolactin (PRL) were measured before and after gonadotrophin releasing hormone (GnRH) and thyrotrophin releasing hormone (TRH) stimulation in 17 patients with endometrial cancer, in 15 patients with uterine fibroids, in 11 patients with ovarian cystadenomas or cancer and in 14 age-matched controls. The women with fibroids had a low FSH level and a diminished FSH response to GnRH but an excessive PRL response to TRH while the other patient groups did not differ from the controls. The results indicate no relation between pituitary function and endometrial or ovarian tumour.

IN mice, prolonged treatment with gonadotrophins can result in the formation of ovarian tumours (Ely, 1959; Li and Gardner, 1949). In humans, some ovarian tumours are known to contain receptors to gonadotrophins (Davy *et al*, 1977). In the present study, we measured pituitary gonadotrophins and prolactin before and after pituitary stimulation in women with endometrical cancer, uterine fibroids and ovarian tumours.

PATIENTS AND METHODS

Forty-three women with gynaecological tumours were selected for the study (Table I). Seventeen women had Stage I endometrial cancer. Fifteen women had uterine fibroids of varying weights (205 to 910 g). Eleven women had ovarian tumours, nine of them had a serous cystadenoma (weight range 530 to 1700 g) and two had Stage II ovarian cancers. In addition, 14 age-matched women with urinary incontinence or uterine prolapse but no pelvic tumour were studied as controls. Any drug treatment likely to alter pituitary function was discontinued for at least two weeks before the study.

The study was made one or two days before diagnostic curettage or surgery. A venous cannula was inserted at 0730 hours. Thirty minutes later, the first blood samples were taken and 100 μg of synthetic gonadotrophin releasing hormone (GnRH) and 200 μg of thyrotrophin releasing hormone (TRH) were given simultaneously as a rapid intravenous bolus. Further blood specimens were collected at 20 and 60 minutes after the injection. The serum was separated with centrifugation and stored at −20°C. Follicle stimulating hormone (FSH), ance rates are associated with a greater time-to-time stability of circulating levels.

The practical implication of the present studies on PP5 is that a single sample from one individual may not be representative of all samples taken from that individual and that the diagnostic *efficiency* will be increased if serial samples are examined.

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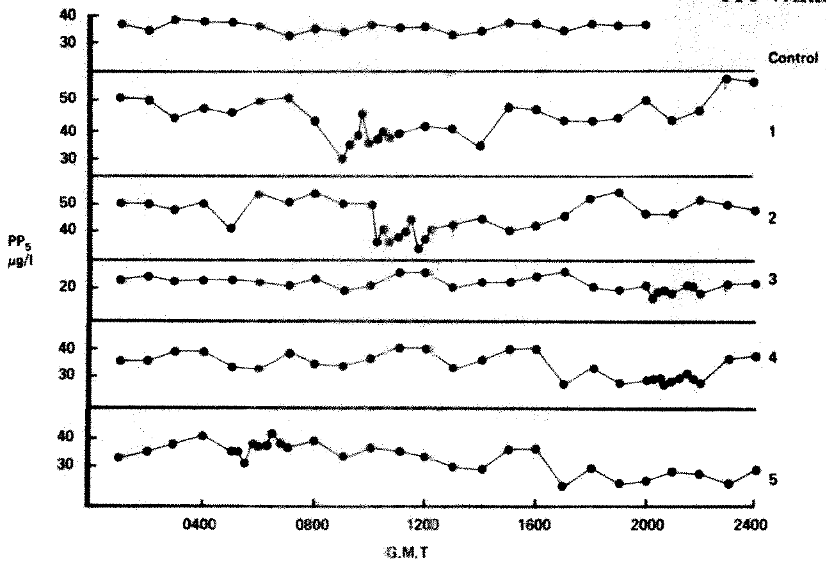

FIG. 1
Serum PP5 levels in five patients over a 24-hour period.

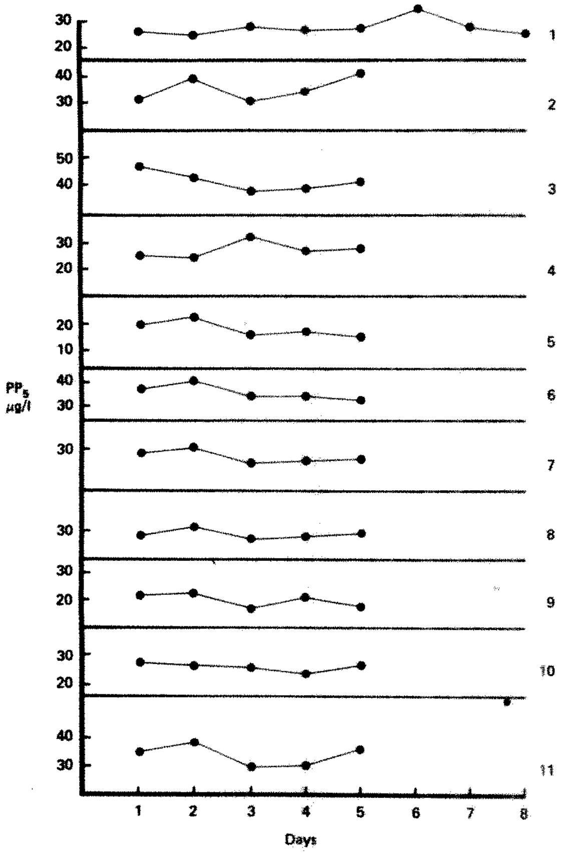

FIG. 2
Serum PP5 levels in 11 patients sampled daily for up to eight days.

of that which could be attributed to the assay, though the variation showed no obvious pattern.

Study 2. The coefficient of variation of serial daily samples from 11 subjects ranged from 5·1 to 15·1 per cent (Table II, Fig. 2). In all cases the variation was in excess of that which could be attributed to the assay.

DISCUSSION

These findings show that there is both a nyctohemeral and day-to-day variation in maternal circulating levels of PP5. However, there is no obvious pattern to the variations and it cannot therefore be described as a rhythm, nor can the variations be related to obvious physiological events such as sleep or meals. The observations are similar to those for placental lactogen (hPL) though the time-to-time variability of both PP5 and hPL is apparently rather greater than that of other placental proteins such as pregnancy specific β_1 glycoprotein (SP_1) and pregnancy associated plasma protein A (PAPP-A); whether this difference is due to technical factors (precision of the assay) or to biological factors such as the plasma half-life or the compartmental distribution is not certain at the present time. However, it is of interest to note that proteins with a relatively short half-life (PP5 and hPL) seem to show rather more variation than those with a longer half-life (SP_1 and PAPP-A) and it may be that slower clear-

TABLE I

Nyctohemeral variation of maternal serum PP5 levels in 5 subjects examined over a 24-hour period

		Patient samples				Control samples (n = 20)				
Patient number	Weeks of gestation	No. of samples	Mean PP5 (μg/l)	Coefficient of variation (per cent)	Variance (H)	Mean PP5 (μg/l)	Coefficient of variation (per cent)	Variance (C)	'F' value (H/C)	Probability (P)
1	36	30	43·7	15·8	47·61	49·7	4·2	4·41	10·79	< 0·001
2	39	31	45·9	12·6	33·64	53·7	4·2	4·84	6·95	< 0·001
3	40	30	22·3	14·1	9·86	24·6	3·58	0·88	12·80	< 0·001
4	35	30	35·9	11·2	16·16	42·0	3·05	1·64	9·85	< 0·001
5	37	30	34·9	12·8	20·07	38·1	4·04	2·37	8·47	< 0·001

TABLE II

Day-to-day variation of maternal serum PP5 levels in 11 subjects studied over a 5-day period

		Patient samples				Control samples (n = 20)				
Patient number	Weeks of gestation	No. of samples	Mean PP5 (μg/l)	Coefficient of variation (per cent)	Variance (H)	Mean PP5 (μg/l)	Coefficient of variation (per cent)	Variance (C)	'F' value (H/C)	Probability (P)
1	37	8	27·4	10·8	8·82	30·18	2·9	0·77	11·45	< 0·001
2	40	5	35·4	12·3	18·66	,,	,,	,,	24·23	< 0·001
3	38	5	42·6	8·4	12·81	,,	,,	,,	10·90	< 0·001
4	37	5	28·0	11·0	9·48	,,	,,	,,	12·31	< 0·001
5	36	5	19·6	15·1	8·82	,,	,,	,,	11·45	< 0·001
6	38	5	35·8	8·2	8·70	,,	,,	,,	11·29	< 0·001
7	39	5	27·8	7·8	4·70	,,	,,	,,	6·10	< 0·005
8	35	5	29·6	5·1	2·31	,,	,,	,,	3·00	< 0·05
9	35	5	20·8	10·4	4·66	,,	,,	,,	6·05	< 0·005
10	36	5	26·4	5·8	2·31	,,	,,	,,	3·00	< 0·05
11	35	5	33·6	10·5	12·32	,,	,,	,,	16·00	< 0·001

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THE VARIATION OF MATERNAL BLOOD LEVELS OF PLACENTAL PROTEIN 5 IN LATE PREGNANCY

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Summary

Serum placental protein 5 levels measured in the third trimester of pregnancy showed nyctohemeral and day-to-day variation, but this variation did not follow any recognisable pattern.

PLACENTAL protein 5 (PP5) has recently been isolated from human term placenta and has the electrophoretic mobility of a β_1 globulin, a molecular weight of 36 600 and a carbohydrate content of 19 per cent (Bohn, 1972; Bohn and Winckler, 1977). The development of a specific and sensitive radioimmunoassay (RIA) for PP5 (Obiekwe *et al*, 1979) has permitted the measurement of maternal circulating PP5 levels during pregnancy; this was not previously possible using immunodiffusion techniques (Bohn, 1972; Bohn and Winckler, 1977). In normal pregnancy circulating PP5 concentrations rise from a mean of 23 μg/l at 28 weeks to a plateau with a mean of 32 μg/l at 36 weeks (Obiekwe *et al*, 1979).

We report here the nyctohemeral and day-to-day variations of PP5 in maternal blood in the third trimester of pregnancy.

METHODS

Sixteen normal patients in the third trimester of pregnancy gave informed consent to one of two studies.

Study 1—variation during a 24-hour period

A total of 151 serum samples was collected from 5 patients at hourly intervals for 22 hours, and at 15-minute intervals for the remaining 2 hours.

Study 2—variation during a 5-day period

A total of 58 serum samples was collected from 11 patients on 5 or more consecutive days.

Serum PP5 was determined by radioimmunoassay as described previously (Obiekwe *et al*, 1979). Each assay included 20 repeat determinations on a single sample. The value for within-assay variation derived from this was compared with the variation observed in samples from individual patients by the 'F' test.

RESULTS

Study 1. The coefficient of variation of serial samples from 5 subjects studied during a 24-hour period ranged from 11·2 to 15·8 per cent (Table I, Fig. 1). In all cases the variation was in excess

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(Table II). There was no apparent association between parity, mode of delivery, birth weight, placental weight, or sedation during labour.

DISCUSSION

The half-life of SP_1 following delivery of the placenta, as measured by radioimmunoassay, has a range of values which is similar to that reported by other authors, despite the fact that all previous studies were based on immunoprecipitation assays. This is surprising as the half-life of α_2 mobile glycoprotein which is also detected in the precipitation assays is shorter than that of SP_1 (B. Teisner, personal communication). However, analysis of the present series shows that each subject has her own characteristic apparent half-life. Furthermore, as is the case for human placental lactogen (Pavlou *et al*, 1972), it is not statistically valid to calculate a mean from the observed half-lives from different individuals as observed by other authors. It is possible, therefore, that a systematic difference in the results using different assays is obscured by the very large variation between individual subjects.

The individual differences could possibly be attributed to variation in clearance according to the physiological state of the subject (position, degree of physical exertion, and sedation), though there is no direct evidence for this. In view of the relatively long half-life, it is unlikely that the differences could be due to variation in the exact time of placental separation.

ACKNOWLEDGEMENTS

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TABLE I

Previous studies on the half-life of pregnancy-specific β_1 *glycoprotein* (SP_1) *in the circulation*

Author	Number of patients studied	Total number of assays	Interval between samples (hours)	Duration of sampling (days)	Estimated half-life of SP_1 (hours)
Bohn (1974)	3	12	12–48	5	30–40
Tatra *et al* (1975)	8	42	12–24	5	24–48
Lin *et al* (1976)	55	89	24	16	20–40
Klopper *et al* (1978)	12	158	5 minutes—daily	10	21·5±9·87 (SD)

TABLE II

Clinical characteristics of 10 women at delivery in relation to the half-life of pregnancy-specific β_1 *glycoprotein* (SP_1) *after delivery of the placenta*

Patient No.	Parity	Mode of delivery	Analgesia during delivery	Birth weight (g)	Placental weight (g)	Half-life of SP_1 (hours)
1	P	Vaginal	Pethidine	2940	550	20
2	P	Vaginal	Pethidine	3410	620	29
3	P	Vaginal	Epidural	3330	595	40
4	M	Vaginal	Epidural	2610	550	38
5	P	Vaginal	Epidural	3390	610	17
6	M	Vaginal	Epidural + GA	3170	475	32
7	M	Vaginal	Pethidine	4160	690	29
8	M	LSCS	Epidural	4100	550	40
9	P	Vaginal	Nil	3380	800	24
10	P	LSCS	GA	3560	650	45

P = Primipara. M = Multipara. LSCS = Lower segment Caesarean section. GA = General anaesthetic.

TABLE III

The decline of circulating levels of pregnancy-specific β_1 *glycoprotein* (SP_1) *after delivery of the placenta in 10 women.* SP_1 *levels are expressed as a percentage of the level determined immediately before delivery*

Time after delivery (hours)	Patient number									
	1	2	3	4	5	6	7	8	9	10
8	77·3	75·0	90·6	94·5	67·9	78·5	98·0	79·4	68·4	74·1
16	63·6	79·1	78·1	72·2	49·1	73·2	63·4	76·4	57·9	60·5
24	54·5	52·3	62·5	63·8	37·3	55·4	54·8	67·6	41·1	61·7
32	47·7	47·2	58·1	61·1	35·8	50·0	41·9	61·8	35·3	56·8
40	47·7	43·1	50·0	45·0	33·9	41·1	26·9	47·1	37·9	46·9
48	36·4	34·7	37·5	40·0	33·9	39·3	22·6	45·1	28·4	46·9
56	32·3	24·4	36·7	36·1	30·1	33·9	22·6	39·2	16·8	44·4
64	34·1	20·8	26·2	34·4	27·5	33·2	20·4	36·3	19·5	35·8
72	24·5	18·1	29·3	28·9	21·5	26·1	13·4	35·3	18·9	30·1
84	23·2	16·1	23·7	22·2	22·6	21·1	15·1	25·5	9·5	—
96	12·7	11·1	14·7	10·5	12·5	14·6	10·2	15·9	6·3	—
108	7·3	5·5	9·4	6·9	7·9	16·1	—	11·8	4·9	—
120	5·7	4·7	7·5	—	—	—	—	8·0	—	—

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DISAPPEARANCE OF PREGNANCY-SPECIFIC β_1 GLYCOPROTEIN FROM THE MATERNAL CIRCULATION AFTER DELIVERY

BY

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Summary

It is likely that there are systematic differences between circulating pregnancy-specific β_1 glycoprotein (SP_1) levels measured by radioimmunoassay and immunoprecipitation systems. We have re-investigated the decline in circulating levels of SP_1 following delivery of the placenta. Serial blood samples were collected for 120 hours from 10 women following Caesarean section or vaginal delivery at term. The apparent half-life of SP_1 after delivery ranged between 17 and 45 hours.

SEVERAL groups have studied the disappearance of circulating pregnancy-specific β_1 glycoprotein (SP_1) after delivery at term. There is general agreement that the half-life of this protein in the circulation is of the order of one to two days (Table I), but all previous studies were performed using immunoelectrophoresis and immunodiffusion assays. Recently Teisner *et al* (1978) have described the identification of a high molecular weight glycoprotein (molecular weight 200–400 000, α_2 electrophoretic mobility) which can interfere with the precise measurement of SP_1 using immunoprecipitation assays; by contrast, the radioimmunoassay measures predominantly authentic SP_1 (Teisner *et al*, 1979). Since it is likely that the high molecular weight material has a different half-life, we have re-investigated the clearance of SP_1 following delivery of the placenta using a highly specific radioimmunoassay (Gordon *et al*, 1977).

METHODS

Ten women with normal term pregnancies were recruited for study (Table II). Venous blood was obtained immediately before delivery and further samples were obtained at 8-hour intervals until 72 hours, and then at 12-hour intervals until 120 hours after delivery. Serum was separated within two hours of collection and stored at −20°C until assay.

SP_1 was measured using a radioimmunoassay (RIA) described previously (Gordon *et al*, 1977).

RESULTS

Blood levels of SP_1 decreased slowly after delivery (Table III). The estimations of the half-life of SP_1 were made from a 'line of best fit' drawn according to the declining levels of SP_1 in each patient with respect to time, and the estimated half-lives ranged from 17 to 45 hours of some placental proteins may be greater in the retroplacental space than in the peripheral circulation, and it is notable that both the placenta and myometrium are rich in enzymes. Third, there may be a technical artefact in collection, such as contamination with amniotic fluid. The latter is the most likely explanation, since the phenomenon was observed with two undoubtedly placental specific proteins, and one protein of totally different origin. These findings clearly indicate the need to interpret biochemical findings in the so-called 'retroplacental blood' with great care.

ACKNOWLEDGEMENTS

We gratefully acknowledge the assistance of Mrs J. Sooby, Mrs A. McCrae and J. Brandt.

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Smith, R., Klopper, A., Hughes, G., and Wilson, G. (1979): *British Journal of Obstetrics and Gynaecology*, **86,** 119.

In the present study we report the concentrations of four placental proteins: hPL, placental protein 5 (PP5), SP$_1$, and human chorionic gonadotrophin (hCG), and one normal serum component, α_2 macroglobulin, in blood obtained from the retroplacental space and in the peripheral circulation at term delivery.

METHODS

Peripheral venous blood was obtained from 20 women immediately before vaginal delivery (9 patients) or delivery by Caesarean section (11 patients). At Caesarean section, blood was aspirated with a syringe from the space immediately behind the placenta. At vaginal delivery blood was taken from the maternal surface of the delivered placenta. Serum was separated within one hour of collection and aliquots stored at −20°C.

Measurements of hPL, PP5, SP$_1$ and hCG were made by radioimmunoassay described previously (Letchworth *et al*, 1971; Gordon *et al*, 1977; Obiekwe *et al*, 1979; Crowther *et al*, 1979). The α_2 macroglobulin levels were measured by rocket immunoelectrophoresis (RIE) as described by Laurell (1972).

RESULTS

The ratio of retroplacental to peripheral concentrations of the four placental proteins and α_2 macroglobulin is shown in Figure 1. Levels of hPL and PP5 in the retroplacental space were always higher than those in the peripheral blood, the median ratio being 3·39 for hPL and 4·83 for PP5. Levels of SP$_1$ and hCG in the retroplacental space were lower than those in the peripheral blood, the median ratios being 0·84 for SP$_1$ and 0·83 for hCG. The level of α_2 macroglobulin in the retroplacental blood was usually lower than in the peripheral circulation, the median ratio being 0·91.

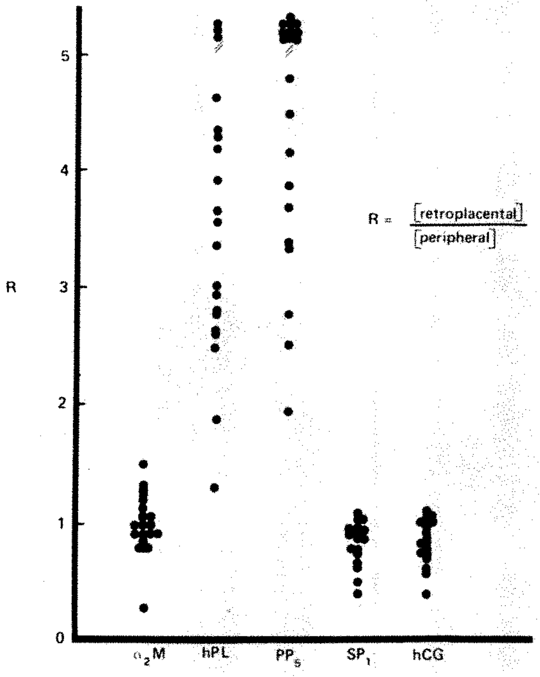

FIG. 1

The ratio of concentrations of α_2 macroglobulin (α_2M), human placental lactogen (hPL), placental protein 5 (PP5), pregnancy specific B$_1$ glycoprotein (SP$_1$) and human chorionic gonadotrophin (hCG) in retroplacental blood in relation to those in the peripheral circulation in 20 subjects.

DISCUSSION

If placental proteins are produced exclusively by the syncytiotrophoblast, there must be a gradient of concentration from the retroplacental space to peripheral blood. The slope of the gradient will vary with the clearance rate of the protein in the mother, being greatest for materials of short half-life (e.g. hPL and PP5; half life 15 to 30 minutes), and least for materials of long half-life (e.g. SP$_1$ and hCG; half-life 20 to 40 hours). In the latter cases the actual rate of secretion is so low that the gradient may not be detectable given the imprecision of current assays. Materials secreted at sites other than the uterus and its contents should, of course, show no gradient.

The present studies show a clear gradient for the proteins of short half-life, hPL and PP5, and confirm previous findings on hPL (Klopper and Hughes, 1978). However, in agreement with earlier findings on SP$_1$ (Smith *et al*, 1979), they show a *reverse* gradient for two proteins of long half-life, SP$_1$ and hCG, and a similar pattern with a non-placental protein, α_2 macroglobulin. There are three possible explanations of this finding. First, synthesis may occur in a site distal to the retroplacental space, though under these circumstances there would be no reason for a gradient in either direction. Second, the clearance

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THE RELATION BETWEEN THE CONCENTRATION OF PLACENTAL SPECIFIC PROTEINS IN RETROPLACENTAL AND PERIPHERAL BLOOD

BY

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Summary

Concentrations of four placental proteins: human placental lactogen (hPL), placental protein 5 (PP5), pregnancy specific β_1 glycoprotein (SP_1) and human chorionic gonadotrophin (hCG), and a normal serum component, α_2 macroglobulin, were measured in the peripheral circulation and in blood obtained from the retroplacental space in 20 women at term delivery. Levels of hPL and PP5 were higher in the retroplacental blood than in the peripheral circulation in all patients. By contrast, levels of SP_1 and hCG were consistently lower in retroplacental blood than in the peripheral circulation. Similarly, levels of α_2 macroglobulin were lower in the retroplacental blood. It is suggested that this 'reverse' gradient is a technical artefact. These findings are discussed in relation to synthesis of placental proteins in a site distal to the retroplacental space, and the introduction of a technical artefact in the collection of samples.

THE evidence that many of the pregnancy 'specific' placental proteins are produced by the trophoblast is based on the isolation of these molecules from the placenta, together with localisation studies demonstrating their presence in the syncytiotrophoblast. Further evidence is provided by the existence of a gradient of concentration from retroplacental space to uterine vein to peripheral circulation. This has been clearly demonstrated for placental lactogen (hPL) (Klopper and Hughes, 1978; Klopper *et al*, 1979) and it was surprising, therefore, when studies on pregnancy specific β_1 glycoprotein (SP_1) revealed no gradient, or even a gradient in the reverse direction (Klopper and Hughes, 1978; Smith *et al*, 1979). On the basis of these findings, Klopper *et al* (1979) and Smith *et al* (1979) have suggested the following possible sources of SP_1: (i) migrating trophoblast in the myometrium; (ii) trophoblast in the lining of the spiral arteries; or (iii) the maternal liver, with secondary absorption by the trophoblast.

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relatively high levels occur in the placenta. This fundamental difference is reflected by the fact that there were no obvious changes in either the blood or tissue levels of PP2 during pregnancy, or in the ratio between them.

Of the trophoblast specific proteins, the pattern of hCG is unique inasmuch as the levels in early pregnancy are considerably higher than those in late pregnancy (Tables I and II). Despite this, hCG shares with other trophoblast proteins the fact that the ratio of maternal levels to placental tissue levels is greater in late than early pregnancy, presumably due to the increase in absolute mass of placental tissue.

The absolute tissue concentrations of hPL and SP_1 showed an apparent increase with gestation, those of hCG a decrease, and PP5 showed no change (Table II). The findings with the first three are compatible with other information on these materials, while that on PP5 is slightly surprising since the expected pattern should be similar to that of hPL and SP_1 (Obiekwe *et al*, 1979). However, if the observations are correct, and it should be noted that the recorded PP5 levels in placental tissue are very close to the sensitivity limits of the assay, then they would indicate that PP5 cannot be readily classified with other protein secretory products of trophoblast. It is of interest in this respect that Bohn (1976) originally described PP5 as a non-secretory protein (though this is now disputed; Obiekwe *et al*, 1979), and that evidence has been presented that PP5 may be related to coagulation processes in the intervillous space (Grudzinskas *et al*, 1979 *a* and b; Obiekwe *et al*, 1979).

There is no simple explanation for the differences in blood:tissue ratios between hPL, hCG and SP_1. Superficially it would be attractive if these were related to the half-lives of the hormones, yet this is clearly not the case since hCG and SP_1 have very similar clearance rates but very different blood:tissue ratios. Nor does the change in ratio during pregnancy relate to half-life, since the change is least for hCG and greatest for SP_1. Furthermore, given that there must be an inverse relation between half-life and secretion, the rate of release of hPL (half-life 0·25 to 0·3 hours) should be at least 100 times greater than that of SP_1 (half-life 30 to 40 hours). If there were a fixed ratio of secretion to tissue stores, then the blood-tissue ratio of SP_1 should be around 100 times that of hPL, yet in late pregnancy the actual ratio (Table III) is greater than this.

In conclusion, these studies show, albeit indirectly, that there are wide variations in the mechanism of secretion of different trophoblast proteins, and that there are striking changes at different stages of gestation. How these findings relate to the clinical interpretation of maternal blood levels is not known, but they contain at least the hint that there may be substantial differences between products, and that clinical results obtained with one material may not be easily extrapolated to another.

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The placental tissue was thawed and divided into small pieces, and washed three times in phosphate buffered saline (PBS) (50 mM, pH 7·5). One gram of wet tissue was suspended in 5 ml PBS and homogenized for 30 minutes with an electric homogenizer (MSE Ltd., England). After centrifugation at 1800 *g* at 4°C for 30 minutes the supernatant was removed and the precipitate homogenized with a further 5 ml PBS. The two supernatants were pooled and stored at −20°C until assayed.

The measurement of hCG, hPL, SP_1, ferritin, and PP5 was performed by radioimmunoassay as described previously (Crowther, *et al*, 1979; Grudzinskas *et al*, 1977; Obiekwe *et al*, 1979).

RESULTS

The circulating concentrations of hPL, SP_1 and PP5 were higher during late pregnancy than early pregnancy, that of hCG was lower, and ferritin levels showed no difference (Table I). Placental tissue levels of hPL and SP_1 were higher in late pregnancy, hCG levels were lower, and ferritin and PP5 showed no change (Table II). The ratios between the mean serum concentration and the mean tissue concentration have been calculated for each protein (Table III); only the ratio for PP2 fails to show a substantial rise between early and late pregnancy.

DISCUSSION

The proteins examined in this study included four which are known to be specific products of the trophoblast (hCG, hPL, SP_1 and PP5) and one (ferritin PP2) which is not specific although

TABLE I

Levels of placental proteins in maternal serum in early and term pregnancy

	No. of patients	Protein concentration (ng/ml), Mean (and range)				
		hCG	hPL	SP_1	PP2	PP5
Early pregnancy	5	3900 (2400–5000)	56·2 (14–122)	15 200 (6300–23 500)	25·3 (10·7–41·5)	<2 <2
Term pregnancy	5	270·6 (96–628)	5300 (3000–7600)	318 000 (190 000–420 000)	21·4 (7·3–47·4)	27·7 (5·4–45)

TABLE II

Concentrations of placental proteins in placental tissue in early and term pregnancy

	No. of patients	Protein concentrations (µg/g wet weight), Mean (and range)				
		hCG	hPL	SP_1	PP2	PP5
Early pregnancy	5	88·4 (24·5–120)	54·3 (15·4–96)	25·3 (1·2–51·5)	63·3 (9·0–220)	2·2 (1·1–2·9)
Term pregnancy	5	2·3 (1·3–4·5)	545·4 (404–732)	52·9 (29·9–91)	50·6 (15–75·5)	1·8 (1·4–2·1)

TABLE III

The ratio of mean maternal serum concentration to mean placental tissue concentration of placental proteins in early and term pregnancy

	hCG	hPL	SP_1	PP2	PP5
Early pregnancy	0·044	0·001	0·6	0·0004	<0·001
Term pregnancy	0·117	0·0097	6·01	0·0004	0·0154

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CIRCULATING LEVELS OF PREGNANCY PROTEINS IN EARLY AND LATE PREGNANCY IN RELATION TO PLACENTAL TISSUE CONCENTRATION

BY

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Summary

The concentrations of human chorionic gonadotrophin (hCG), human placental lactogen (hPL), pregnancy specific β_1 glycoprotein (SP_1), ferritin (PP2) and placental protein 5 (PP5) were examined in maternal serum and placental tissue in early and late pregnancy. The circulating concentration of hPL, SP_1, and PP5 were higher during late pregnancy than early pregnancy, that of hCG lower, and ferritin (PP2) levels showed no difference. Placental tissue levels of hPL and SP_1 were higher in late pregnancy, hCG levels lower, and ferritin (PP2) and PP5 showed no change. The ratio of the concentration in maternal serum to that in placental tissue increased during pregnancy for all proteins with the exception of ferritin. It is proposed that the mechanism of secretion of trophoblast specific proteins varies widely and that this should be taken into account in the clinical interpretation of circulating levels in the mother.

THE concentrations of placental specific proteins in the maternal circulation have been examined in a wide variety of physiological and pathophysiological situations (Chard, 1976; Klopper and Chard, 1979). Yet there is virtually no information on the relation between levels in maternal blood and tissue levels in the placenta itself, despite the fact that such information might provide a useful background to both biological and clinical studies on these materials.

We report here the concentrations of five placental proteins in maternal blood and placental homogenates collected in the first and third trimesters of normal pregnancy.

METHODS

Venous blood was obtained from five patients immediately before surgical termination of pregnancy at 10 to 12 weeks gestation, and from five patients at the time of delivery at 38 to 40 weeks gestation. Serum was separated within one hour and stored at −20°C until assayed. Placental tissue (5 to 6 g) was obtained at surgical termination of pregnancy. After removal of obvious blood and other products of conception, tissue was excised from a central area. Placentae obtained at term deliveries were treated similarly, and the tissue was stored at −20°C.

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concentration in the uterine vein (173 units/ml) and in the peripheral vein (176 units/ml) was very nearly the same and evidently the inflow from the placenta is too slow to raise the local concentration. The mean concentration of the retroplacental blood (93 units/ml) was only half that of the peripheral blood. The possibility that this is due to dilution of the retroplacental blood with fetal fluids such as amniotic fluid which has a much lower concentration of PAPP-A, can be discounted. Placental lactogen (hPL) which is also present in much lower concentration in fetal fluids was measured at the same time in these subjects and it was found that this protein was present in much higher concentration in the retroplacental blood than in the peripheral blood.

DISCUSSION

In the only other study of PAPP-A in normal pregnancy published so far (Lin *et al*, 1974*b*), a rising concentration right up to term was also found. This is surprising. Placental weight curves tend to flatten in the last 2 to 3 weeks and so do many parameters of placental function such as hPL concentration. This consistent rise of PAPP-A in late pregnancy may be a fortunate feature from the point of view of its use as a measure of placental function as it may make it easier to detect a decline in the production of the protein. This prospect is further enhanced by the remarkable steadiness of the concentration from day to day in the same subject.

The odd distribution of PAPP-A in the maternal circulation is difficult to reconcile with its direct passage into the intervillous blood from the chorionic villi. Immunofluorescent studies have localised the protein in the cytoplasm of the villous trophoblast (Lin and Halbert, 1976). Of course this does not mean that it is produced there; the chorionic villi may be absorbing it from the retroplacental blood. Such a suggestion seems to us inherently unlikely. It is conceivable that the intervillous space is not the only or even the main point of entry of PAPP-A into the maternal circulation. There are other means by which PAPP-A could enter maternal blood. Attwood and Park (1961) describe trophoblastic embolism to the lungs. They point out that the process increases with increasing age of the placenta and is exaggerated by labour; a suggestion which fits with our findings of higher PAPP-A values in labour. A further possibility arises from invasion of the decidua and the myometrium by nonvillous trophoblast (Robertson *et al*, 1975). If substantial amounts of PAPP-A are being released directly into the maternal tissue by dissolution of non-villous trophoblast, our findings on the half-life of PAPP-A should be regarded in a new light, for all source of PAPP-A inflow will not be cut off by delivery of the placenta. It may also have some bearing on the function of the protein. It may be that its point of entry reflects the site of action. There are good reasons for supposing that local factors play a part in preventing the rejection of the trophoblast by the maternal tissues.

The assay of PAPP-A is simple. Given the antiserum it can be set up in any hospital laboratory. If it is a placental product, its concentration in the maternal blood may bear some relevance to placental function. The usefulness of the assays in obstetric disease should be examined. We should be happy to make available supplies of our antiserum for clinical investigation.

ACKNOWLEDGEMENTS

Our work in this field was made possible by the generosity of Drs T. M. Lin and S. P. Halbert of the University of Miami. They made available to us a supply of PAPP-A antiserum which made it possible for us to isolate the antigen and prepare our own antiserum. R.S. was supported by the Medical Research Council who also defrayed the costs of the work through a grant to A.K. Mrs Pamela Cunningham gave us technical assistance and secretarial help was supplied by Miss Gina Cowie.

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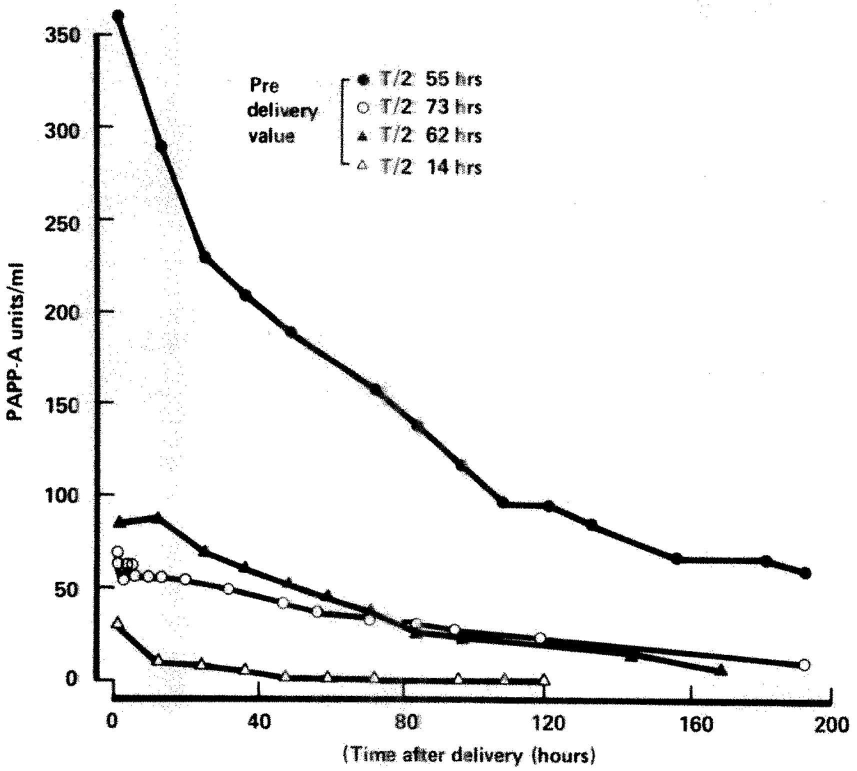

FIG. 3

The decline in PAPP-A concentration after delivery in four patients.

It may be that the steadiness of PAPP-A concentration is a reflection of its relatively long half-life. The decline in PAPP-A after delivery is shown in four subjects in Figure 3. The average half-life was 51 hours. It should be noted that this figure is based on the assumption that no further inflow of PAPP-A into the maternal compartment takes place after the delivery of the placenta. The findings may not be a true representation of the survival time of the protein in the circulation.

No PAPP-A could be found in cord artery, cord vein or amniotic fluid within the range of our method of measurement. Evidently, the secretion of PAPP-A is directed to the maternal, not the fetal compartment. Its distribution in the maternal compartment is shown in Figure 4. The concentration in peripheral blood is eight times greater than in the peritoneal fluid. If the latter is at all representative of the interstitial fluid as a whole, the passage of PAPP-A out of the blood vessels must be greatly impeded. The mean

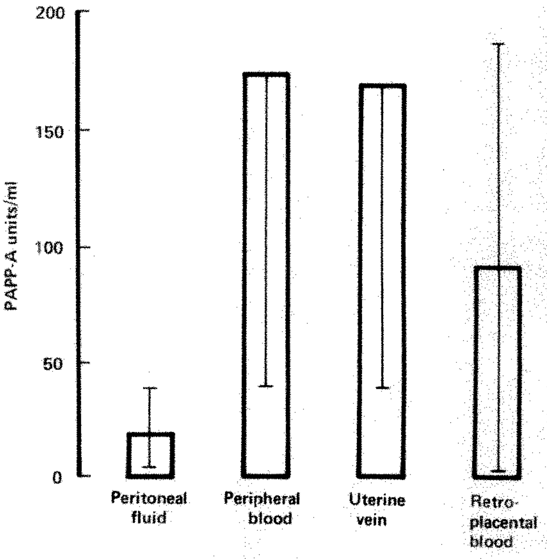

FIG. 4

The concentration of PAPP-A in maternal circulation and peritoneal fluid (average of 10 patients).

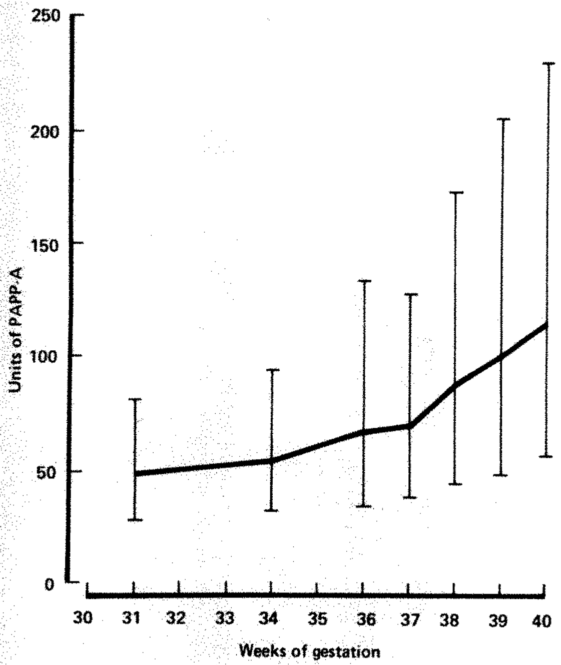

FIG. 1

The mean and standard deviation of PAPP-A in the last 10 weeks of pregnancy shown as a log transformation.

of these a specimen was obtained during labour. As can be seen from Figure 2 the value in labour was higher than the value obtained within the preceding week. Although the mean prelabour value was not significantly different from the mean value in labour it is probable that there is a rise in labour as 11 of the 12 patients had higher PAPP-A concentrations when in labour. The average PAPP-A concentration fell after 286 days gestation but as shown in Figure 2 the mean value in labour in this post-term group was again higher than the value obtaining in the previous week. Blood was obtained during labour in eight of these post-term patients and all showed values which were higher than those in the preceding week.

The day-to-day fluctuations of PAPP-A in nine subjects each studied on seven successive days are shown in Table II. The coefficients of variation ranged from 4 to 11 per cent with an average figure of 7 per cent. PAPP-A concentration was less variable than was that of plasma steroids. Thus plasma oestriol has a coefficient of variation of 15 per cent. The variability of PAPP-A was closely comparable with that of other placental proteins, such as SP_1 which has a coefficient of variation of 5 per cent (Masson *et al*, 1977).

TABLE II

The coefficients of variation in PAPP-A concentration measured in nine subjects over seven days each

Subject	PAPP-A (units)* Mean	SD	Coefficient of variation (per cent)
1	108·4	10·9	10·0
2	76·6	3·4	4·4
3	112·1	7·2	6·5
4	111·4	10·3	9·3
5	64·9	5·4	8·3
6	98·1	4·5	4·6
7	43·7	5·0	11·3
8	43·3	1·8	4·2
9	131·6	9·2	7·0

Mean coefficient of variation 7·3±2·6 per cent

* In arbitrary units giving value of 100 units to a late pregnancy pool.

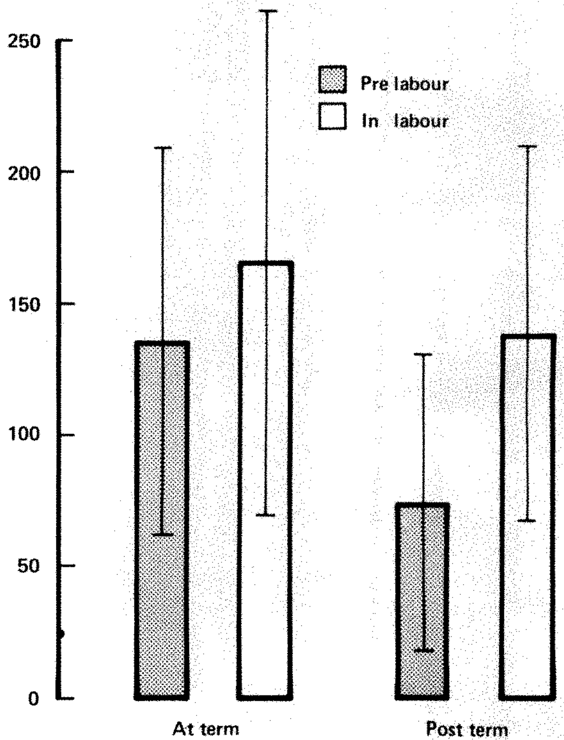

FIG. 2

The mean and standard deviation of PAPP-A before labour compared with the value in labour, in full term and post-term subjects.

protein through the mother by measuring its concentration in retroplacental blood, in the uterine vein, in peripheral vein and in the peritoneal fluid, taking the last as representative of the interstitial space.

EXPERIMENTAL DESIGN

Originally 51 volunteers were recruited. They were segregated in a research antenatal clinic run by AK and RS. Blood was taken at 2 to 3 week intervals from 30 to 36 weeks and at weekly intervals thereafter. A final sample was taken in early labour. On review after delivery it was found that only 34 patients could be regarded as completely normal in that they had no medical or obstetric disease and had given birth to babies with weights between the 10th and 90th centile as determined by the criteria laid down for the Aberdeen obstetric population by Thomson *et al* (1968). The findings we present apply only to these 34 normal pregnancies. The mean ±SD gestation at delivery of these 34 patients was 282 ±7·6 days and the average birthweight was 3395 g. Seven consecutive daily blood samples were collected at the same time of day during the 38th week of pregnancy from nine of the volunteers. Four others took part in the half-life study; blood being drawn at intervals over nine days post partum. Samples were also obtained from various sites in ten other women undergoing elective Caesarean section. These sites were the peritoneal fluid, the antecubital vein, the uterine veins and the retroplacental space, the sampling being done as previously described (Smith *et al*, 1979).

METHODS

The heparinised blood was centrifuged directly and the plasma (3 to 5 ml) stored at −20°C until assayed. To reduce interassay variability all the specimens from a particular study, be it of day-to-day variability or puerperal decline, were assayed together. PAPP-A was measured by Laurell electroimmunodiffusion as described by Bischof *et al* (1979). The antiserum was prepared by injecting purified PAPP-A into rabbits and adsorbing out the resulting antiserum with non-pregnant human serum. The standards were serial dilutions of a pool of late pregnancy serum which was arbitrarily defined as containing 100 units/ml. (PAPP-A standard has since been calibrated against pure PAPP-A and one unit of PAPP-A = 1·506 μg of PAPP-A). In our experience such late pregnancy pools have very similar concentrations of PAPP-A provided sufficient individuals contribute to the pool, and will serve the purpose until an agreed international standard is available.

RESULTS

The changes in PAPP-A concentration in the last ten weeks of pregnancy are recorded in Table I. It can be seen that the concentration rises steadily up to 36 to 37 weeks after which the concentration increases more steeply right up to term. Although, as is evident from the large standard deviations in Table I, there was a considerable spread (roughly an order difference, 20 to 200 units/ml, from the lowest to the highest individuals) the pattern was remarkably consistent. A rising trend was present in everybody and an acceleration in the rate of rise during the last 3 or 4 weeks of pregnancy could be discerned in almost everyone. It has been suggested that biological parameters such as this have a skewed distribution (Chard, 1976) and are best represented as a logarithmic transformation. Such a plot of the data is shown in Figure 1. A similar steep rise in PAPP-A right up to term, with a tendency for more observations to cluster below than above the mean, can be seen in the findings recorded by Lin *et al* (1974*b*).

Nine patients were delivered between 287 and 293 days gestation, the remainder earlier but none before 266 days. Thirteen patients went into labour between 280 and 286 days and in 12

TABLE I

Pregnancy-associated plasma protein A (PAPP-A) concentrations in late pregnancy (in arbitrary units giving value of 100 units to a late pregnancy pool)

Gestation (days)	No. of observations	PAPP-A (units) Mean ±SD
210–230	15	55±27
231–251	20	62±34
252–258	23	84±55
259–265	22	83±48
266–272	31	106±63
273–279	24	123±72
280–286	13	137±74
287–293	8	74±55

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STUDIES ON PREGNANCY-ASSOCIATED PLASMA PROTEIN A IN THE THIRD TRIMESTER OF PREGNANCY

BY

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Summary

The plasma concentration of pregnancy-associated plasma protein A (PAPP-A) was measured in 34 women during the last 10 weeks of pregnancy. From 30 to 36 weeks the concentration of this protein increased steadily. Thereafter the concentration of PAPP-A rose more steeply, the highest amounts being found in early labour. The concentration of PAPP-A in peripheral venous blood and in the uterine vein was much the same. It was less in the retroplacental blood and a great deal less in the peritoneal fluid. The day-to-day variation was small; the coefficient of variation at 38 weeks was only 7·3 per cent. After delivery, the concentration of PAPP-A fell more slowly than other placental proteins and steroids, the average half-life being 51 hours. Although there is no doubt that PAPP-A is a product of the syncytiotrophoblast, our findings suggest that it is not simply secreted by the chorionic villi directly into the intervillous space but makes its way into the maternal circulation by a more circuitous route.

PREGNANCY associated plasma protein A (PAPP-A) is a protein produced by the placenta and secreted into the maternal blood stream in increasing amount as pregnancy advances. It was first isolated five years ago (Lin *et al*, 1974*a*). Until now almost all the work on this protein has been done by this Miami team. They found that it was a relatively large molecule (750 000 daltons) and, by immunofluorescent staining, showed that it was present in the syncytiotrophoblast. The first investigations (Lin and Halbert, 1976) have shown that the concentration of PAPP-A alters in some obstetric diseases. This raises the possibility that measurements of PAPP-A might give an indication of the placental state. In order to explore the changes in disease it is necessary to have a clear picture of the variations which might be encountered in normal pregnancy. We have therefore set out to expand the data on PAPP-A in normal pregnancy. To do so we have measured levels in a cohort of women serially during the last ten weeks of pregnancy. We have also determined the variation from day to day in the same subject and have measured the rate of decline in the plasma concentration after delivery of fetus and placenta. We have traced the spread of the production and compartmental distribution of this enzyme might lead to a better understanding of the regulatory processes directing fetal placental growth and maternal reactions in preventing rejection of the fetus and are in progress in this laboratory.

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TABLE II

Average of polyamine oxidase (PAO) activities in repeated assays one to six weeks apart

Number of patients	PAO activity (nmol/minute/l) Mean ± SEM	
	First assay	Second assay
19	96·7 ± 19·4	92·3 ± 20·8

enzyme present in sheep and bovine sera is inhibited by isoniazid, a typical inhibitor of pyridoxal phosphate containing enzymes. In contrast the PAO extracted from mammalian tissue can be inhibited by quinacrin, an inhibitor of flavin requiring enzymes, but not by isoniazid (Hölttä, 1977). In our study, quinacrin completely inhibited PAO activity in all cases, while isoniazid at the same concentration reduced PAO activity by some 20 per cent.

DISCUSSION

Cell growth and proliferation appears to be associated with increased synthesis and accumulation of the polyamines, putrescine, spermidine and spermine (Tabor and Tabor, 1976; Jänne *et al*, 1978). Inhibition of polyamine synthesis was found to be associated with a marked suppression of DNA synthesis, preceded by a decrease in protein synthesis and a depression in the incorporation of [^{3}H] uridine and [^{14}C] adenine into total RNA (Hölttä *et al*, 1979). Polyamines are present in high concentration in fetal (Jänne *et al*, 1964) and neoplastic tissue (Russell and Snyder, 1968). In the urine of women with normal pregnancies an elevated excretion of putrescine and spermine was observed, with a significant increase in their plasma levels. High concentrations have also been found in the amniotic fluid either in free form (Russell *et al*, 1978), or as polyamine conjugates (Chan *et al*, 1979). These observations are thought to be compatible with an *in vivo* function for these compounds in the regulation of embryonic growth and development.

On the other hand, the polyamines spermidine and spermine inhibited the synthesis of DNA in murine spleen cells stimulated with phytohaemagglutinin (PHA), pokeweed mitogen, concanavalin A and bacterial lipopolysaccharide, and in PHA-stimulated thymic lymphocytes, but only in the presence of either calf or fetal calf serum. There was no inhibition in parallel cultures with normal human or mouse serum. Polyamines in the presence of fetal calf serum inhibit the ability of murine lymphocytes to recognise irradiated allogenic cells and also the induction, but not the expression, of the cytolytic lymphocyte response. It was also shown that this *in vitro* suppressive effect was reversible and was not based on cytotoxicity. These observations suggested that the activation of the inhibitory properties of spermine was due to an amine oxidase activity, which is abundant in ruminant sera but shows very little activity in normal human serum (Allen *et al*, 1977; Byrd *et al*, 1977; Rijke and Ballieux, 1978). Human pregnancy serum after the 15th week of pregnancy also possesses the ability to convert spermine and a lesser extent putrescine to an inhibitor of PHA-induced lymphocyte transformation, while neither fetal cord sera nor normal human sera had such an activity (Gaugas and Curzen, 1978). It was postulated that the product of the interaction of polyamine and bovine or human pregnant sera might represent 'a physiological immunoregulatory mechanism' and might mediate 'a successful subversion of the host immune system in those individuals bearing tumours or outbred fetuses' (Byrd *et al*, 1977).

Our results confirm that there is a spermine oxidising enzyme present in the pregnant serum with very low levels during the first trimester, but a substantial and sustained rise throughout mid- and late pregnancy. The great individual variations in the activity might be explained either by the cross-sectional nature of the study, or by the biological variability of expression, since the reproducibility of the assay procedure was found to be highly satisfactory. This PAO appears to be a flavoprotein, since we were able to show complete inhibition of its activity in the pregnant sera by quinacrin, a known inhibitor for flavoproteins, while isoniazid a pyridoxal phosphate enzyme inhibitor has far less effect. It might, therefore, be assumed that the PAO present in pregnancy sera is similar to that found in the rat liver and differs from that present in bovine and other ruminant sera (Morgan, 1979). Further investigations to detect the site of samples were incubated with [^{14}C] labelled spermine and after deproteinisation with trichloroacetic acid, the polyamines in the reaction mixture were separated by chromatography on strong cation exchange resin, which separated [^{14}C] labelled products from unreacted substrate. The radioactivity in each fraction was then determined by liquid scintillation counting in a Toluene-Triton scintillation mixture (2:1 v/v) containing 5 g *PPO* and 0·05 g *POPOP* per litre.

Inhibition of PAO activity

Quinacrin (N^4-(6-chloro-2-methoxy-9-acridinyl)-N′, N′-diethyl-1, 4-pentanediamine) and isoniazid (4-pyridinecarboxylic acid hydrazide) at 10^{-4}M final concentration were used in the inhibition studies. Serum samples were preincubated with one or other inhibitor for 15 minutes at 37 °C before addition of labelled substrate.

RESULTS

PAO activity in pregnancy serum

PAO activity in pregnancy serum increased significantly with time with an approximately linear trend from the 10th week on (slope = 4·74±0·25 nmol/minute/l per week of gestation, t(115) = 18·96, p <0·001; Fig. 1). The mean values and range of serum PAO activity at each trimester are shown in Table I. In only three patients (one in the 10th and two in the 14th week) was no activity demonstrable. No activity was found in male control sera and in only one case did we detect very low activity (less than 20 nmol/minute/l) among the control non pregnant female sera.

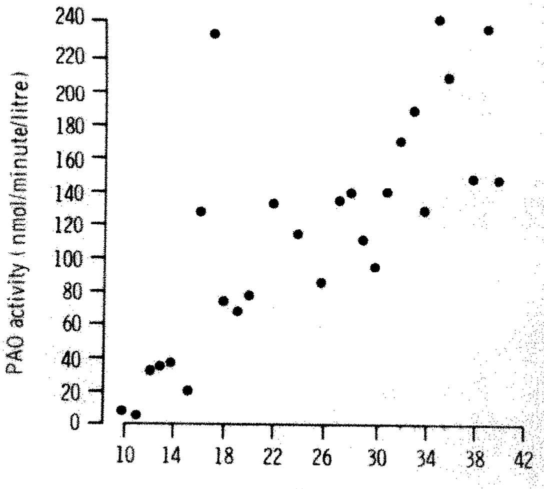

FIG. 1

Serum polyamine oxidase activity in pregnancy. Each point is the mean value for that time period. Slope = 4·74±0·25 nmol/minute/l); t (115) = 18·96; p <0·001.

Reproducibility

To test the reproducibility and reliability of the assay procedure, we repeated the estimations in 19 cases. The interval between the first and second assay varied from one to six weeks, and the sera tested covered a range of 14 to 38 weeks gestation. The difference in the average values of the measured activities between the first and repeated assays is within 5 per cent (Table II).

Inhibition of PAO activity

It has been shown (Tabor *et al*, 1954) that the

TABLE I

The geometric means and range of serum polyamine oxidase (PAO) activity in the three trimesters of pregnancy

	I. trimester (10–13 weeks)	II. trimester (14–26 weeks)	III. trimester (27–40 weeks)
Number of patients	14	46	57
PAO activity (nmol/minute/l) Mean ±SEM	28·46±7·73	84·76±9·73	153·36±11·7

I– II P <0·01
II–III P <0·001
I–III P <0·001

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POLYAMINE OXIDASE ACTIVITY IN HUMAN PREGNANCY SERUM

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Summary

The existence of a spermine oxidizing enzyme was established in human pregnancy serum by a radiochemical method, and a cross-sectional study of its quantitative profile between 10 and 40 weeks gestation was undertaken. Though there was a wide scatter of values, the rise in the average activity was continuous and highly significant. The flavoprotein inhibitor, quinacrin, inhibited the enzyme activity, while the pyridoxal phosphate inhibitor, isoniazid, had no significant inhibitory effect suggesting that the enzyme is of tissue origin. The possible role of polyamines and their oxidation in physiological immunoregulation is discussed.

THE role of polyamines in the organization of tRNA structure and activity and the correlation of elevated polyamine synthesis with rapid growth phenomena appear now to be well established (Russell *et al*, 1978; Cohen, 1978). *In vitro* studies suggest that the action of polyamine oxidase (PAO) on polyamines produces inhibitors of cell proliferation, which are not cytotoxic (Byrd *et al*, 1977; Allen *et al*, 1977; Rijke and Ballieux, 1978). It has also been shown that human pregnancy serum in the presence of excess biogenic polyamines can inhibit lymphocyte transformation *in vitro*, suggesting that specific PAOs present in pregnancy serum but absent from non pregnant human sera were the converting factors (Gaugas and Curzen, 1978). Hitherto, however, no direct analyses of the PAO activity of human pregnancy serum have been reported. Because of the possible singificance of the polyamine-PAO interaction in the regulation of growth processes and lymphoproliferation, we did cross-sectional estimations of the PAO activity in the serum of healthy pregnant women throughout pregnancy.

MATERIALS AND METHODS

The PAO activity was estimated in a cross-sectional study in the sera of 117 healthy pregnant women between 10 and 40 weeks gestation. Blood was taken once from each of the women during an antenatal visit by venepuncture using sterile disposable syringes, transferred into glass bottles and allowed to clot for 15 minutes at room temperature. Serum was separated by centrifugation and stored at −20 °C. Control samples were taken under similar conditions from five healthy men and 17 age-matched, non pregnant women.

PAO activity assay

The serum PAO activity was estimated essentially as described by Morgan (1979). The

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PAO activity in the peripheral serum taken after spontaneous delivery is significantly higher than in serum obtained during elective Caesarean section, can be explained by the effect of the uterine activity. The PAO activity found in the maternal circulation might be the consequence of a leakage rather than secretion into the maternal blood and is not high enough to cause a generalized suppression of the maternal cellular immunity although some decrease may occur.

As to the site of the production of PAO, our findings are not conclusive. The procedures we have used to obtain and prepare homogenates of placental and decidual tissue are somewhat crude and since the decidual cells in the basal plate are in close relation to the trophoblast and trophoblastic cells may migrate into the decidua (Dallenbach-Hollweg and Nette, 1964), the possibility of incomplete separation of these tissues cannot be excluded. Intracellular identification of the enzyme by immunochemical methods would give more reliable data on cellular and subcellular localisation and the separation of PAO from retroplacental fluid for specific antibody formation is under way in this laboratory. The effect of various PAO concentrations on the multiplication of different spontaneously growing cells is also under investigation.

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immune responsiveness during pregnancy, based on evidence which includes depressed *in vitro* lymphocyte response to mitogens (Finn *et al*, 1972; Purtilo *et al*, 1972); decrease in the size of the lymph nodes draining the uterus; depression of germinal centres and a marked reduction in their cellular content (Nelson *et al*, 1973) are among others.

It has been reported that human pregnancy serum inhibits mitogen-stimulated lymphocyte proliferation (Walker *et al*, 1972; Jones *et al*, 1973; Figueredo *et al*, 1979). Crude human chorionic gonadotrophin (hCG) preparations had similar effect (Adcock *et al*, 1973), while highly purified hCG did not influence the lymphocyte response to mitogens, suggesting that the lymphocyte suppression observed was due to additional unidentified substances present in the crude hormone preparations (Caldwell *et al*, 1975; Gundert *et al*, 1975). Alpha-fetoprotein was found to effectively suppress T-cell mediated reactions but not B-cell responses *in vitro* (Murgita *et al*, 1978). Also important are the observations of Jones *et al* (1973) and Figueredo *et al* (1979), that maternal peripheral serum taken at early stages of pregnancy failed to inhibit phytohemagglutinin (PHA) induced lymphocyte proliferation or *in vitro* mixed lymphocyte reaction, while late pregnancy serum had marked suppressive effects.

On the other hand, lymphocytes separated from the blood taken by suction from the uterus in the first trimester of pregnancy were significantly less responsive to PHA stimulation than lymphocytes separated from the peripheral blood of the same patients (Fuchs *et al*, 1977). These observations suggest that in early pregnancy an immunsuppressive factor is operating within the uterus but is not yet detectable in the peripheral circulation. The reports cited, however, have not identified the extent, nature or mechanism of the inhibitory activity expressed by maternal serum on the maternal cell-mediated immune response.

In recent years it has been shown that nanogram quantities of the polyamines SPD and SPM markedly inhibit murine and human T and B lymphocyte stimulation but only in the presence of fetal calf serum (FCS) (Allen *et al*, 1977; Byrd *et al*, 1977 and 1978). FCS is known to possess abundant PAO activity (Tabor *et al*, 1954) capable of converting SPD and SPM into other active moieties that are active inhibitors of lymphocyte proliferation. It has been shown that the reaction is reversible, non-cytotoxic and the target cell is the actively differentiating cell (Byrd *et al*, 1978). It is unlikely that the inhibitory effects could be explained by the direct action of the amino aldehydes produced by the enzyme or of acrolein as suggested by Tabor *et al* (1954) and Alarcon (1970), since these substances are toxic and their effect would be irreversible. Cell toxicity and inhibition of cell multiplication are separate and distinct parameters of cell biology. The observations of Byrd *et al* (1978) suggest that the product(s) of the SPM–PAO interaction act rather on the membrane of the target cell than intracellularly, but the details of this process are as yet unknown.

Polyamines and PAOs are widely distributed in plants, fungi, bacteria and mammalian tissues (for reviews see Byrd *et al*, 1978 and Morgan, 1979), but on the basis of the experimental data available, enhanced levels of both polyamine and PAO would appear to be essential for their suppressive effect on cell proliferation to be apparent. Russell *et al* (1978) have shown that the human placenta is rich in polyamines, the values being higher in early compared to term placentas. On the other hand, urinary and serum levels of these substances increase as pregnancy progresses. Our present and previous data (Illei and Morgan, 1979) indicate that PAO activity also increases during human pregnancy. On the basis of these results we believe that the increased polyamine–PAO production during human pregnancy is of maternal origin, is pregnancy associated and might contribute to a decrease in the maternal immune reactivity. This is in accordance with the observation of Gaugas and Curzen (1978), who found that human pregnancy serum from 15 weeks gestation in the presence of exogenous polyamine inhibited the PHA-stimulated proliferation of rat thymic lymphocytes. Our present data indicate that the PAO level in the retroplacental serum is significantly higher than that found in the maternal uterine or peripheral venous blood serum and lend support to the suggestion that the principal site of the polyamine–PAO action is the placental bed and that this interaction might form the basis of a *local immunological barrier* and might operate very early in pregnancy. Our observation, that the

TABLE II

Polyamine oxidase (PAO) activity in the maternal and fetal compartment in triplet pregnancy

Source of sample	PAO activity (nmol/minute/l)
Maternal	
cubital vein	834
uterine vein	1386
retroplacental fluid	6564
Umbilical vein	0
artery	0

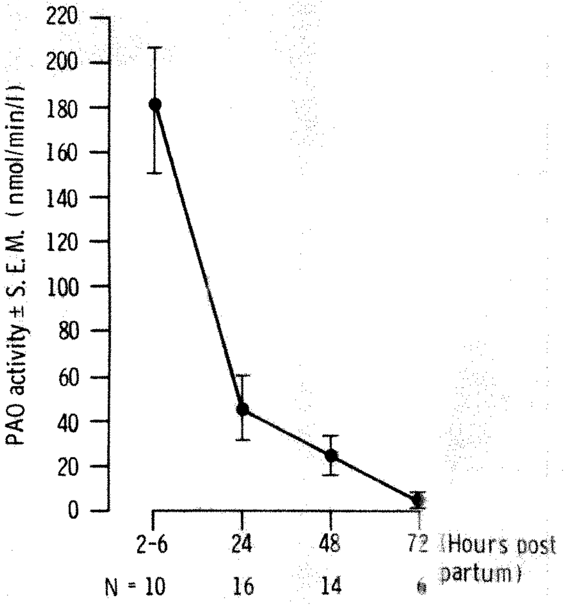

FIG. 1

Average serum PAO levels in the early postpartum period.

were substantially higher in every compartment than those observed in singleton pregnancies.

The maternal serum enzyme activity fell rapidly after delivery (Fig. 1), the half life being approximately 24 hours (Fig. 2).

PAO activity in cord serum

No enzyme activity was found in any of the cord serum samples taken either during elective Caesarean section or after spontaneous delivery.

PAO activity in tissue homogenates

In the decidual homogenates, significantly higher PAO activity was found than in the placental extracts (P < 0·02; Table III).

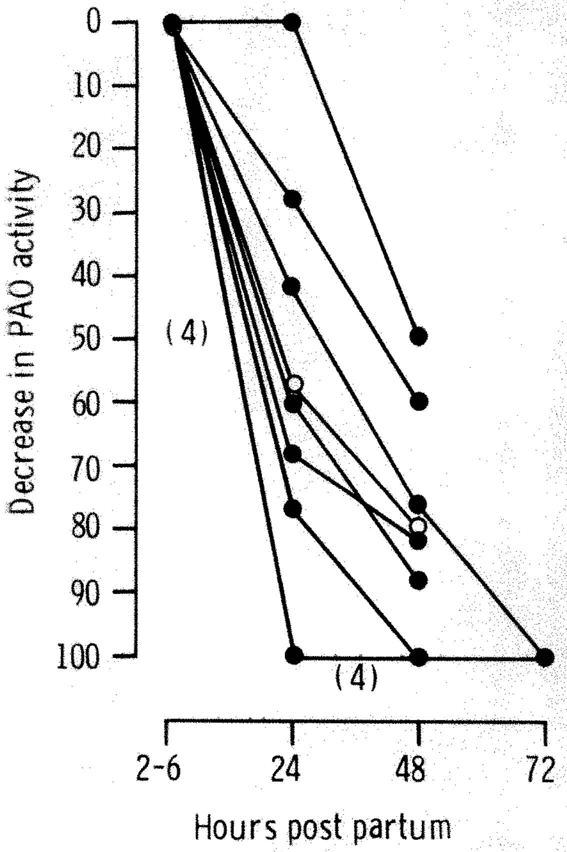

FIG. 2

Serial estimation of PAO activity in the serum of 10 patients in the early postpartum period.

● = Individual patients
○ = Average

TABLE III

Polyamine oxidase (PAO) activity in placental and decidual extracts

Source of sample	N	PAO activity (nmol/minute/g wet tissue) Mean ± SEM
Placenta*	7	0·600 ± 0·196
Decidua*	4	5·442 ± 2·176

* P < 0·02

DISCUSSION

It is now generally accepted that the conceptus can be considered as an intrauterine allograft which the mother, for some reason, fails to reject. Several hypotheses have been put forward to explain this phenomenon: diminished the third stage of labour (five volunteer patients) and during elective Caesarean section (eight patients) in normal pregnancies. In the latter patients, just before the uterus was opened blood was also drawn from the uterine vein. Blood was collected from umbilical artery and vein before delivery of the placenta.

The retroplacental serum, composed mainly of intervillous blood plus decidual and placental interstitial fluid, was collected as described by Klopper and Hughes (1978) from 8 patients after elective Caesarean section and from 11 patients after spontaneous delivery.

In the postpartum period blood was withdrawn serially 2 to 6, 24 and 48 hours from the cubital vein of 10 patients after spontaneous delivery. Additional blood specimens were also obtained 24 hours (six patients) and 48 and 72 hours (four patients) after delivery.

All the samples were allowed to clot for 15 minutes at room temperature. Serum was separated by centrifugation and stored at −20°C.

PAO activity assay

The serum PAO activity was estimated as described previously (Morgan *et al*, 1979; Illei and Morgan, 1979) and the results expressed in nmol/minute/litre.

Tissue extracts

Placental and decidual tissue samples obtained during elective Caesarean section were blotted, weighed and transferred to cold 10 mM Tris buffer pH 7·4 (9 ml/g wet tissue). The tissues were finely chopped with sterile scissors (or a scalpel) and homogenised in a glass vessel fitted with a motor-driven Teflon pestle. After centrifugation of the homogenate, enzyme activity in the supernatant fluid was assayed and the results expressed as nmol/minute/g wet tissue.

For statistical analysis the Student's t-test was used.

RESULTS

PAO activity in maternal serum

The average PAO activity in peripheral maternal serum taken at the time of elective Caesarean section was similar to that found in the uterine venous blood serum of the same patients (Table I). These values corresponded to the enzyme activities measured in the serum of normal pregnant women during the last weeks of pregnancy (153·36±11·7 nmol/minute/l) (Illei and Morgan, 1979). The average PAO level in the serum of parturient women at the end of normal spontaneous labour was, however, significantly higher (P <0·02, Table I).

On the other hand, the PAO activity in the retroplacental serum was markedly elevated compared to the peripheral and uterine venous blood serum, the differences being highly significant (P <0·001).

One patient (Table II, data not included in Table I) had an elective Caesarean operation because of a triplet pregnancy; the PAO values

TABLE I

Polyamine oxidase (PAO) activity in maternal and fetal compartments

Source of sample	Caesarean section N	Caesarean section PAO activity (nmol/minute/l) Mean ±SEM	Spontaneous labour N	Spontaneous labour PAO activity (nmol/minute/l) Mean ±SEM
Maternal				
cubital vein	7	146±30·6*	5	266±47*
uterine vein	7	152±32·9	–	–
Retroplacental serum	7	4817±909·8	11	4872±701·5
Umbilical cord				
vein	7	0	7	0
artery	3	0	–	–

* P <0·02

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THE DISTRIBUTION OF POLYAMINE OXIDASE ACTIVITY IN THE FETOMATERNAL COMPARTMENTS

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Summary

Polyamine oxidase activity was measured in different compartments of the fetomaternal unit by a radiochemical method. The activity in the retroplacental serum (mainly of intervillous origin) was 20 to 30 times higher than in maternal uterine or peripheral venous blood sera. No activity was found in the fetal cord blood sera. The enzyme level in the maternal peripheral sera fell to undetectable levels within 72 hours post partum. Preliminary data indicate that the enzyme might be produced by the decidua rather than by the placenta. It is suggested that the enzyme may constitute an important part of a supposed local immunological barrier formed at the placental bed to help to protect the fetal allograft from maternal immune rejection through a local suppressive effect on maternal cellular immunity.

In a previous paper (Illei and Morgan, 1979) we described the presence of a spermine oxidising enzyme (polyamine oxidase, PAO) in pregnant serum with low levels during the first trimester, but a substantial and sustained rise throughout mid- and late pregnancy. We also raised the possibility that this enzyme might play an important role in the regulatory processes directing maternal immune reactions in preventing the rejection of the fetus (Illei and Morgan, 1979). This assumption was based on previous reports that the polyamines, spermidine (SPD) and spermine (SPM), reacting with calf serum PAO reversibly suppress mitogen-stimulated lymphocyte proliferation (Allen *et al*, 1977; Byrd *et al*, 1977; Rijke and Ballieux, 1978; Gaugas and Curzen, 1978). Other workers (Fujita *et al*, 1976; Giles *et al*, 1977; Russel *et al*, 1978) found significant increases in urinary polyamine levels during pregnancy with a tendency to return to normal within 10 days post partum. Substantial increases in the polyamine content in the placenta have also been reported (Russell and Durie, 1978), the levels being higher in early pregnancy than at term and it was suggested that the lower levels at term may be due to 'the presence of high levels of monoamine oxidases in the placenta', but this assumption has not been investigated.

In the light of these findings it seemed important to study the serum PAO activity in the maternal and fetal compartments at term and in the maternal peripheral blood serum post partum.

Materials and Methods

Sera

Blood was taken from the cubital vein during causes a moderate fall in diastolic pressure, but it also may help venous return which leads to a rise in systolic pressure and thus an increase of differential (pulse) pressure. This is why ritodrine differs from other beta-mimetics, in not causing marked hypotension.

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The significant rise in heart rate helps to increase further the cardiac output, which is already high from the chronotropic and positive inotropic effects of beta-stimulation.

The patients tolerated even high doses well, which may be in part due to the proven increase in myocardial efficiency.

Our data show that the various haemodynamic changes recorded produce a higher maternal cardiac output and demand a higher maternal heart work load. The drug should therefore be used at least in lower dosage in patients with cardiac disease. Further research is needed to determine the dose and administration which, with a minimum of effect on the cardiovascular system, will maintain its proven tocolytic effect.

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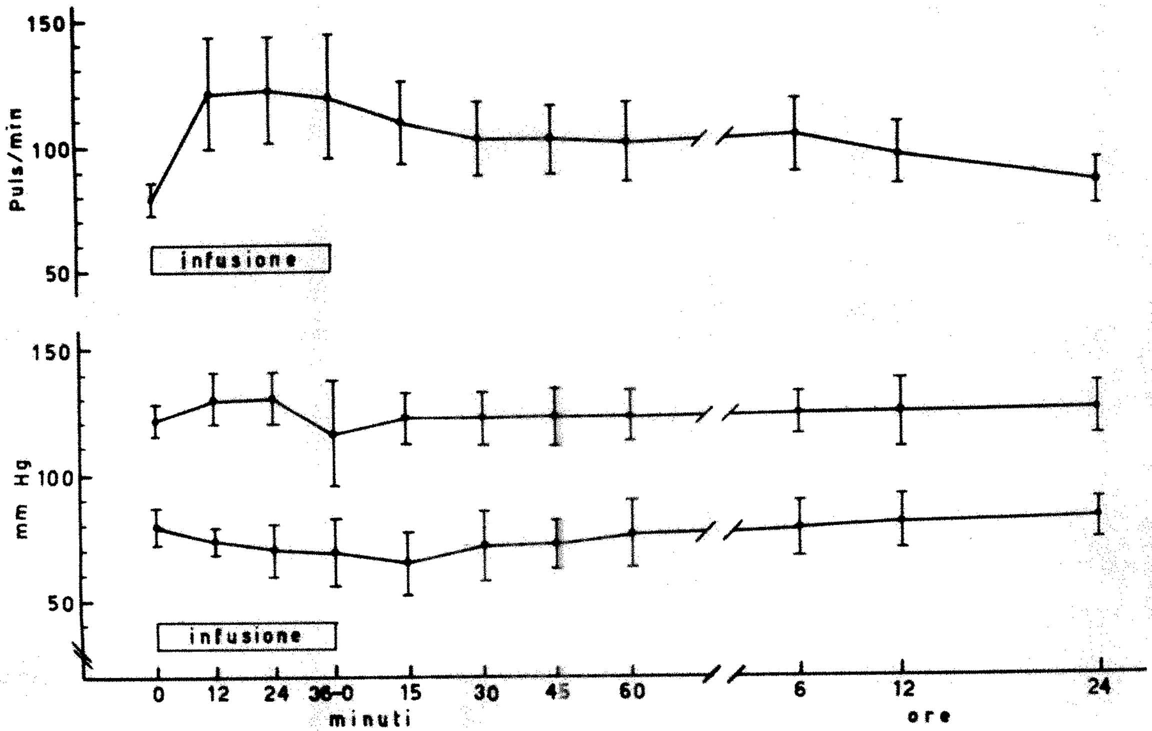

FIG. 4

Heart rate and systolic and diastolic arterial pressure during and after infusion with Ritodrine.

especially that of ICT, may be due to the positive chronotropic action of beta-stimulants, but it may be caused partly by left ventricular tone overcoming the contractile efficiency of the myocardium; it is useful to have haemodynamic confirmation of such data.

Shortening of the expulsive period (TET) is essentially related to rise in heart rate.

Plethysmography clearly confirms the peripheral vasodilatory action of the drug: in all tracings during and immediately after infusions with ritodrine, there was a marked rise in peripheral blood-flow.

In two cases studied by the same method but using double dosage (800 μg/minute), we noted a surprising tendency to reduction of the width of the plethysmographic wave. We hope therefore to make a further study to investigate these last results; could they represent a paradoxical alpha mimetic reaction?

The pressure variations caused by the drug are moderate and principally on the diastolic pressure, evidently related to peripheral arteriolar dilatation.

The many cardiovascular effects noted, some of which like tachycardia, are undesirable, always appeared to be transitory: indeed in no patient was it possible to find significant changes 24 hours after the end of the administration of the drug.

CONCLUSIONS

The existence of statistically significant changes, even if transitory, in some cardiovascular parameters force us to reflect on the haemodynamics of patients taking betamimetic drugs such as ritodrine. It is particularly necessary to do so in a period of pregnancy in which the maternal cardio-vascular system has already made major adaptations. The drug has its greatest effects on the haemodynamic system, maternal heart rate and on peripheral vascular resistance.

The fall in peripheral vascular resistance

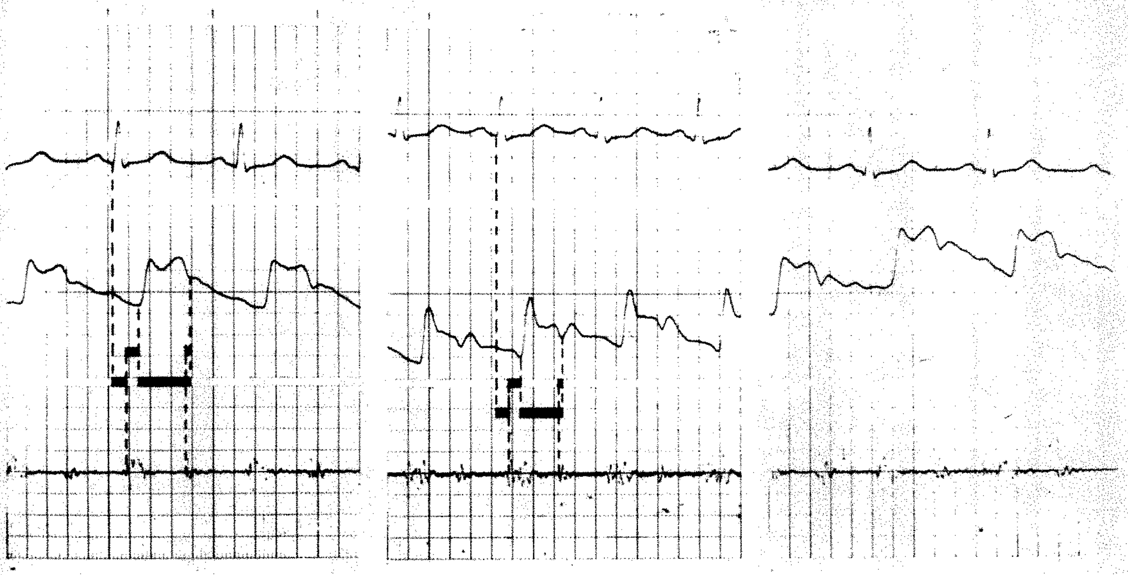

FIG. 2
Polygraphic tracings obtained before (a), at 24 minutes (b) and at 12 hours (c) after starting ritodrine infusion.

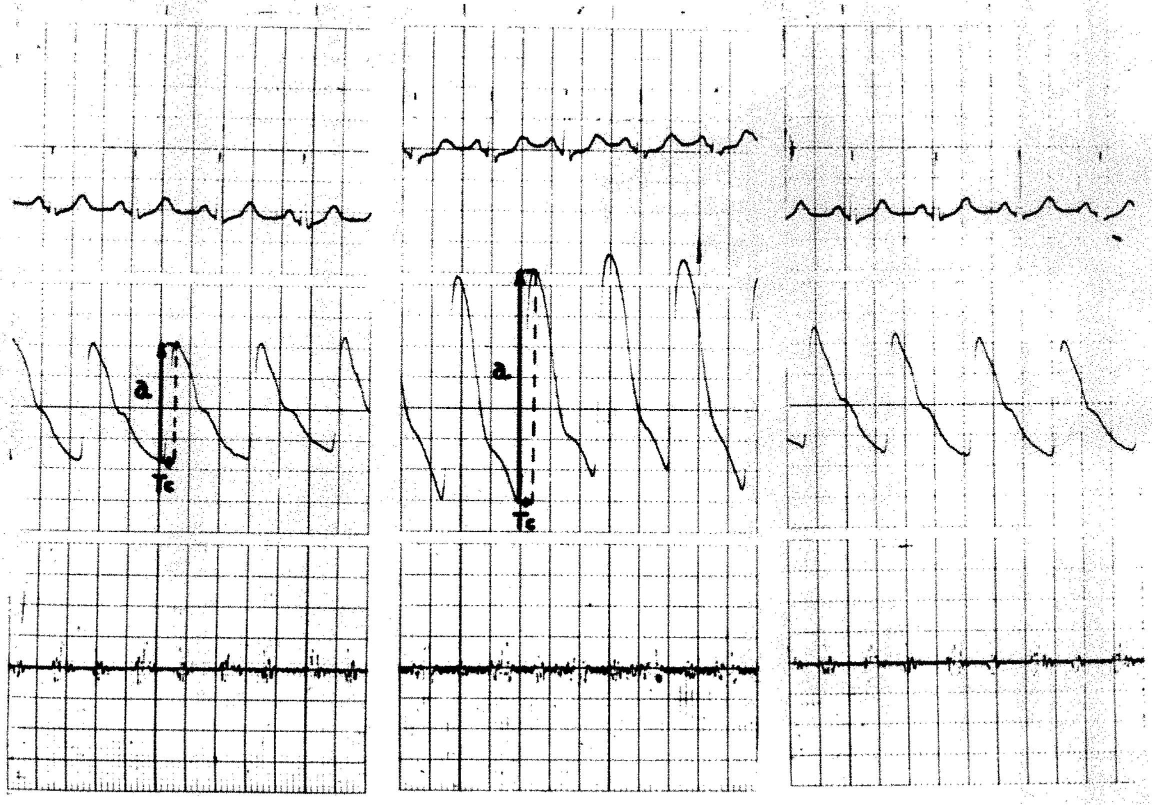

FIG. 3
Photoplethysmographic tracing obtained before infusion (a), at 30 minutes (b) and at 12 hours (c) after the end of infusion. The considerable increase of the plethysmographic wave width is evident 30 minutes after the end of the infusion, and the return of basal values 12 hours after the end of infusion.

Interruption of the administration of the drug, interestingly, did not cause the heart rate to fall immediately to the pre-infusion levels; instead there was a slow, gradual fall, the initial values being reached only 12 hours after the end of the infusion (Fig. 4).

Arterial pressure

Changes in arterial pressure, measured by ultrasound, were similar to those recorded by Nochimson *et al* (1974).

Systolic pressure varied only slightly, and not significantly. There was a small rise during the infusion followed by a gradual return to initial values after its cessation. Diastolic pressure underwent an obvious, but not statistically significant decrease which was particularly marked at the end, and 15 minutes after the end, of infusion. It then rose gradually to the initial value, which was reached at about 6 to 12 hours after infusion (Fig. 4).

DISCUSSION

The data from the polyplethysmographic study on the maternal cardiovascular effects of ritodrine administration to women in late pregnancy indicate some areas in which clinical evaluation is needed before starting treatment with the drug.

Ritodrine causes a significant rise in the heart rate and thus cannot be considered, at least for the dosages administered by us, devoid of beta-1 stimulating activity. This is in agreement with most previous research; no drugs have yet been synthesized which can stimulate or selectively inhibit beta-1 or beta-2 receptors. They may act principally, but not wholly, on one or the other. The decrease in pre-expulsive times (QS2+ICT),

*m. The figures in parenthesis represent percentage change from the baseline value**

Time after end of ritodrine infusion					
30 minutes	45 minutes	60 minutes	6 hours	12 hours	24 hours
60·0 (−)	60·0 (−)	60·0 (−)	60·0 (−)	60·0 (−)	60·0 (−)
43·7±18·0 −32·77%)	48·7±13·1 (−25·10%)	48·7±13·1 (−25·10%)	55·1± 7·7 (−15·24%)	60·0± 5·0 (−7·70%)	64·2± 1·5 (−1·23%)
03·7±11·0 −17·04%)	108·7±13·1 (−13·04%)	115·1± 7·7 (−7·92%)	115·1± 7·7 (−7·92%)	120·0± 5·5 (−4·0%)	124·2± 1·5 (−0·64%)
27·5±18·8 (−7·15%)	225·0±18·9 (−8·17%)	225·0±20·8 (−8·17%)	235·0±20·5 (−4·08%)	245·0±19·6 (−)	245·0±19·6 (−)
2·19± 0·2 +11·73%)	2·05± 0·2 (+4·59%)	2·05± 0·2 (+4·59%)	2·04± 0·2 (+4·08%)	2·04± 0·1 (+4·08%)	1·97± 0·1 (+0·51)%
31·2±14·5 -122·85%)	28·5±14·1 (+103·57%)	26·7±11·3 (+90·71%)	18·0± 6·5 (+28·57%)	14·2± 5·5 (+1·42%)	14·2± 3·9 (+1·42%)
02·2±14·9 +29·04%)	106·2±12·1 (+34·09%)	103·0±14·8 (+30·05%)	91·3± 9·6 (+15·27%)	80·1± 8·0 (+1·13%)	80·0± 8·7 (+1·01%)
21·2±13·7 (−)	121·2±11·0 (−)	118·7±10·3 (−2·07%)	122·3±12·2 (+0·90%)	122·5± 9·0 (+1·07%)	121·9±10·0 (+0·57%)
73·7±10·3 (−7·87%)	75·0± 0·1 (−6·25%)	73·7±13·1 (−7·87%)	76·6±10·1 (−4·25%)	78·7±10·3 (−2·50%)	80·0± 7·0 (−)

ılsion time (TET), of the relation between expulsive period and pre-ejection period (TET/PEP), of plethysmography, of fferent times starting from the beginning of ritodrine infusion.

standard deviations and the percentage change from the baseline value.

There was a reduction of QS2, ICT and of PEP (QS_2 + ICT). The shortening of the pre-ejection times was statistically significant ($p < 0{\cdot}05$) with respect to the values before treatment (Fig. 2a), starting from the first measurement during infusion at 12 minutes, and reaching a minimum value at the 24th minute (Fig. 2b).

It then started to lengthen towards the pre-treatment values (Fig. 2c) which were reached 12 hours after the beginning of the infusion.

Similar variations were observed for the TET values which were minimal 24 minutes after the beginning of infusion and returned to the pre-treatment values after 12 hours. The Blumberger index did not show significant statistical modification.

Photoplethysmography

The digital plethysmographic data (Fig. 3a) reported on Table I together with heart rate and the arterial blood pressure changes, showed a constant and marked increase in the width of the wave, maximal 30 minutes after the end of the infusion (Fig. 3b). The wave width than gradually fell, until by the 6th hour after infusion the values were close to those before treatment. Pretreatment levels were regained after 12 hours (Fig. 3c).

Heart rate

The maternal heart rate changed significantly during administration of the drug. The basal rate of 79·2 beats/minute rapidly rose to a maximum average of 122·3 beats/minute, 24 minutes after the start of the infusion. The increase was statistically significant ($p < 0{\cdot}01$).

Cardiovascular and haemodynamic measurements before, during and after rito

		Time after onset of ritodrine infusion			
Measurement	Baseline value	12 minutes	24 minutes	36 minutes	15 minutes
QS2 (m second)	60·0	56·6± 5·7 (−5·66%)	55·8± 5·9 (−7·00%)	55·9± 7·0 (−6·83%)	56·2± 7·5 (−6·33%)
ICT (m second)	65·0±10·0	43·2±15·2 (−33·54%)	35·0± 5·0 (−46·16%)	37·5± 2·6 (−42·31%)	40·0± 7·9 (−38·46%)
PEP (m second)	125·0±10·0	100·0±20·0 (−20·0%)	90·0±18·8 (−28·0%)	92·3± 8·3 (−26·16%)	96·2±12·5 (−23·04%)
TET (m second)	245·0±37·8	193·3±41·6 (−21·11%)	180·0±34·6 (−26·53%)	200·0±43·2 (−18·37%)	207·5±35·8 (−15·31%)
TET/PEP	1·96± 0·3	1·95± 0·4 (−)	2·00± 0·3 (+2·04%)	2·13± 0·3 (+8·67%)	2·14± 0·3 (+9·18%)
PLETHISMO (mm)	14·0± 1·6	16·6±9·0 (+18·57%)	19·0± 5·5 (+35·71%)	21·5±11·1 (+53·57%)	25·0±11·1 (+78·57%)
PULSE (beats/minute)	79·2± 6·5	120·0±22·9 (+51·51%)	122·3±21·1 (+54·41%)	112·7±24·2 (+42·29%)	106·5±16·5 (+34·47%)
PA MAX (mm Hg)	121·2± 6·2	131·6±10·4 (+8·58%)	131·6±10·4 (+8·58%)	122·5±20·6 (+1·07%)	122·5±11·9 (+1·07%)
PA MIN (mm Hg)	80·0± 7·0	76·6± 5·7 (−4·25%)	70·0±10·0 (−12·50%)	70·0±13·5 (−12·50%)	68·7±13·1 (−14·12%)

* Values of left ventricular deformation time (QS2), of isometric contraction time (ICT), of pre-ejection period (PEP), of heart rate, of systolic and diastolic arterial pressure, with the respective standard deviations and the percentage increase, calcul

(Ote-Galileo mod. C 3 a). From the tracing the most significant left ventricular systolic times were calculated: total electromechanical systole (QS2); isometric contraction time (ICT); pre-ejection period (PEP); total expulsion time (TET) (time between opening and closing of aortic valves); and finally the relation between the expulsive and pre-expulsive period (TET/PEP or Blumberger index).

The peripheral blood flow variations were evaluated indirectly by digital plethysmography. The peak time (Tc), was considered less important than the amplitude of the plethysmograph wave (Fig. 1). A baseline measurement was made immediately before the beginning of the infusion, after an observation period of about 15 minutes. Further measurements were made at 12, 24 and 36 minutes after the start of the ritodrine infusion, and then at 15 minutes, 30 minutes, 45 minutes, 60 minutes, 6 hours, 12 hours and 24 hours after the end of the infusion. The statistical significance of the variations was calculated using the Student's t test.

RESULTS

Polygraphy

In Table I the mean data are reported with the

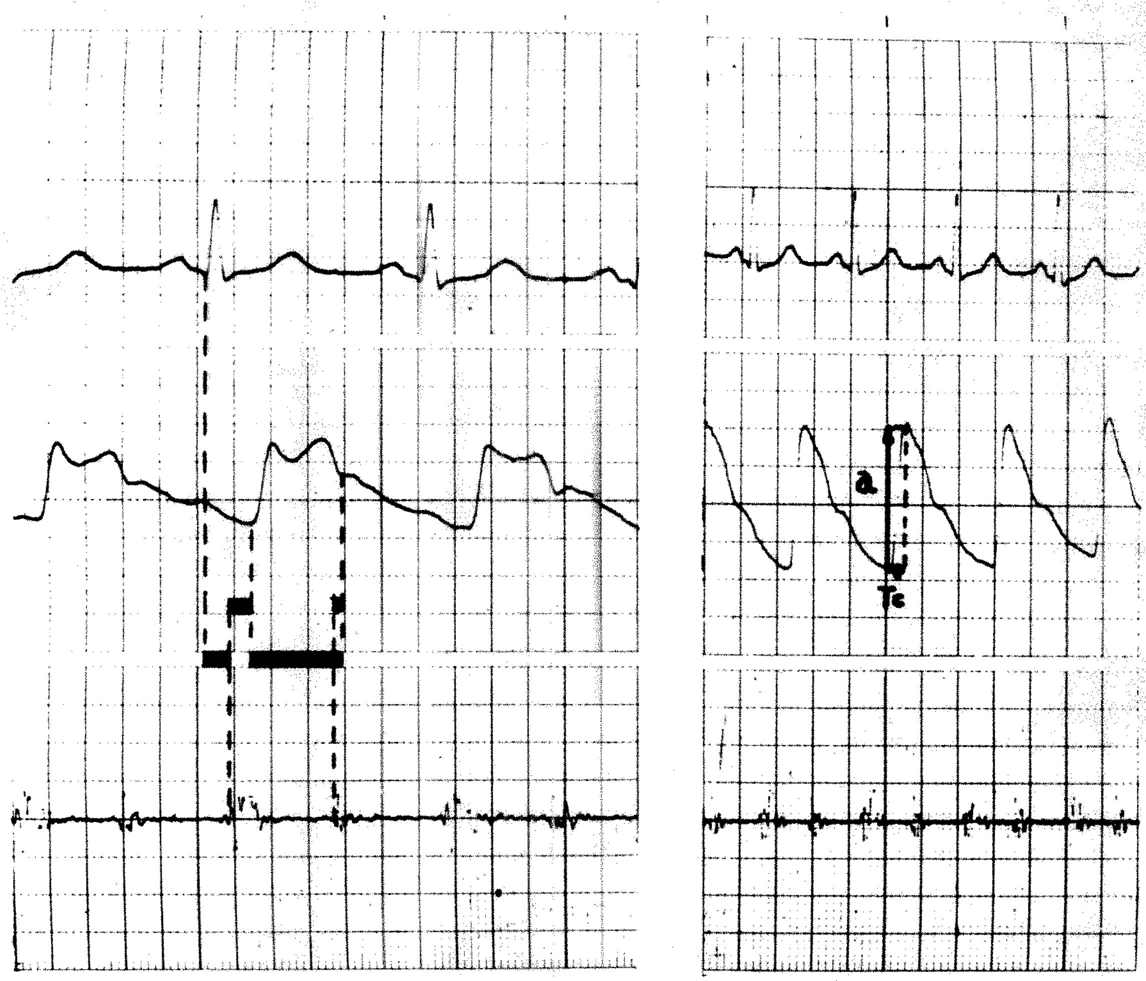

FIG. 1

Basal polycardiographic tests: on the left are shown from top to bottom the electrocardiogram, the carotid pulse and the phonocardiogram; the method of determination of QS2, ICT (QS2+ICT = PEP) and of TET is outlined by dotted lines. On the right from top to bottom the electrocardiogram, the digital plethysmogram and the phonocardiogram are shown; the method of measuring the plethysmographic wave width (a) and the peak time (Tc) are shown.

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POLY-PLETHYSMOGRAPHIC STUDY ON THE EFFECTS OF RITODRINE ON THE CARDIOVASCULAR SYSTEM OF PATIENTS IN LABOUR

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Summary

The effects of ritodrine infusion on the cardiovascular system of six women in threatened or premature labour are reported. In contrast to other betamimetics, ritodrine caused a moderate rise in systolic blood pressure, the corresponding fall in diastolic pressure leading to a widened pulse pressure but no risk of hypotension. Ritodrine caused a rise in cardiac output, and was well tolerated by the patients. Special care should be taken in treating patients with known heart disease.

THE tocolytic action of beta-mimetics has partly fulfilled the considerable obstetric need for drugs capable of blocking uterine contraction, but their use is often limited by hypotension and marked tachycardia, leading to poorer placental perfusion and consequent damage to the fetus. Many sympathomimetic non-catecholamines have been synthesized in the search for a drug with a selective action on the uterine muscle and with negligible cardiovascular and metabolic effects.

The effects of a new betamimetic drug, ritodrine, on the maternal heart and circulation are described.

METHODS

Six patients, aged between 18 and 29 years, admitted to the obstetrics department of the University of Genoa for treatment of premature labour, or in term labour, entered the study. All patients gave informed consent. There were no metabolic or cardiovascular complications during any of the pregnancies. The gestational age on admission varied from 35 to 40 weeks.

Every patient was given $400/\mu g$/minute of ritodrine for 36 minutes by intravenous infusion in physiological saline, using a Holter precision Roller Pump model 912; heart rate, systemic arterial blood pressure, left ventricular dynamics and peripheral blood flow were measured before, during and after the infusion.

Cardio-dynamics were measured using simultaneous external phonocardiograph, and carotid tracings recorded on a 3-channel polygraph

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change its plasma level only slowly in response to production rate variations. Plasma 11-HOCS have a half-life of around 60 minutes (Petersen *et al*, 1955), but as the fetoplacental unit does not contribute significantly to the maternal 11-HOCS level, delivery does not result in a fall in 11-HOCS level, which rises following delivery due to the physical and emotional stress of the second stage of labour (Buchan *et al*, 1973).

Unconjugated E_3 showed increased production during labour. Hull *et al* (1979) suggest that the level of unconjugated E_3 in maternal plasma is determined mainly by placental blood flow, and if this is so then this study indicates that in the patients studied the placental perfusion increased during labour. It is interesting that of all the placental hormones studied the only one to show a sustained rise during labour was unconjugated E_3 which requires the active participation of fetal steroidogenesis for its production. The fetoplacental unit may be stimulated to produce more unconjugated E_3 by the stress of uterine contractions or by the increased level of cortisol in the first and second stages of labour.

The fall in the level of progesterone during labour in this study has been reported by others (Csapo *et al*, 1971 and 1974). However, Okada *et al* (1974) and Yannone *et al* (1968) reported no change in the plasma levels of progesterone during spontaneous labour. The control of production and release of progesterone must be quite independent of that of oestrogens as both in spontaneous premature labour (Tamby Raja *et al*, 1974) and in oxytocin induced labour the plasma level of progesterone fell as the level of oestrogens rose.

The P:E_2 ratio changes seen in this study are of interest when compared with the ratios reported before and during preterm or spontaneous term labour. Hobel *et al* (1975) found a P:E_2 ratio of 8:1 at 37 weeks in normal patients and of 6:1 in patients in spontaneous preterm labour at the same gestation. Tamby Raja *et al* (1974) found that the P:E_2 ratio fell from 15:1 at 36 weeks to 8:1 at 38 weeks and 5:1 at 40 weeks gestation. It may be that the patients in this present study all went past 40 weeks gestation without going into spontaneous labour because their P:E_2 ratio remained too high at 7:1. An explanation of the falling P:E_2 ratio seen during labour in this study is that either the uterine contractions or the rising 11-HOCS levels act on the fetoplacental unit in such a way as to inhibit progesterone production while at the same time stimulating oestrogen production.

The protein hormones hPL and SP_1 appear to be unaffected by either uterine contractions or plasma cortisol levels. The literature with regard to hPL during labour is in dispute whether the level fluctuates widely (Saxena *et al*, 1969), rises (Singer *et al*, 1970), falls (Cramer *et al*, 1971) or remains, as in the present study, within its normal late pregnancy variability (Pavlou *et al*, 1972). There is no published study of plasma SP_1 levels during labour and the absence of any significant change during labour and the very slow postpartum decline contrasts markedly with the pattern of change seen with the other placental hormones.

The results of this study add evidence to support the hypothesis of Liggins (1973). The association between progressive labour, rising 11-HOCS level and a falling P:E_2 ratio is seen, although whether this association is any more than incidental cannot be determined from this study.

ACKNOWLEDGEMENTS

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TABLE I

Plasma levels of placental hormones before, during and after labour

Hormone	Time of sample	Patients 1	2	3	4	5	6	7	8	9	10	Mean	SD	SEM	Difference from previous level Paired t-test
Unconjugated oestriol (nmol/l)	Pre-induction	79	65	77	73	74	67	85	73	79	81	75	5·9	1·9	
	1st stage	113	79	94	89	83	78	109	102	86	107	94	12·3	3·9	Rise p < 0·001
	2nd stage	133	92	129	105	117	94	131	127	98	121	114	15·2	4·8	Rise p < 0·001
	Post partum	19	25	18	20	38	27	39	29	32	36	28	7·5	2·4	Fall p < 0·001
Oestradiol-17β (nmol/l)	Pre-induction	85	97	73	89	94	100	97	104	87	61	88·7	12·5	3·9	
	1st stage	92	104	87	95	107	101	87	106	103	63	94·5	12·7	4·0	Rise p < 0·05
	2nd stage	78	96	64	84	83	73	62	96	87	83	80·6	11·1	3·5	Fall p < 0·01
	Post partum	19	24	17	26	28	12	10	18	16	17	18·7	5·8	1·8	Fall p < 0·001
Progesterone (nmol/l)	Pre-induction	532	730	524	636	682	660	580	690	700	520	625	75·7	24·0	
	1st stage	478	658	430	524	586	700	500	582	660	440	583	103·3	32·7	Fall p < 0·001
	2nd stage	385	478	368	422	510	580	300	411	520	420	439	78·6	24·8	Fall p < 0·001
	Post partum	110	156	98	141	210	220	100	124	165	108	143	44·3	14·0	Fall p < 0·001
Human placental lactogen (µg/ml)	Pre-induction	8·96	4·90	8·75	4·70	7·89	5·20	8·07	6·65	7·25	7·81	7·01	1·50	0·47	
	1st stage	8·83	4·89	9·30	4·52	7·90	5·24	7·93	6·82	7·89	7·45	7·03	1·53	0·48	No change
	2nd stage	8·04	4·85	9·50	4·48	7·96	5·62	7·85	6·31	8·49	6·73	6·98	1·56	0·49	No change
	Post partum	< 1·0	1·09	1·01	< 1·0	1·10	< 1·0	1·20	< 1·0	< 1·0	1·03	1·04	0·06	0·02	Fall p < 0·001
Pregnancy specific β1 glycoprotein (mg/100 ml)	Pre-induction	21·2	10·9	22·6	11·1	24·2	13·0	19·5	18·7	15·4	11·9	16·8	4·74	1·50	
	1st stage	20·8	11·6	21·8	11·3	23·9	13·8	17·5	18·1	15·2	11·8	16·6	4·32	1·36	No change
	2nd stage	20·2	12·5	20·4	11·6	24·2	12·6	18·8	17·5	14·4	10·1	16·2	4·40	1·19	No change
	Post partum	18·7	11·2	18·4	9·8	18·7	11·8	13·5	15·5	13·2	9·7	14·1	3·39	1·07	Fall p < 0·001
11-hydroxycorticosteroids (nmol/l)	Pre-induction	1501	1049	1081	675	1010	792	742	847	712	762	909	237	79	
	1st stage	1595	1656	1248	795	1813	1338	1455	1181	1449	1355	1389	269	90	Rise p < 0·001
	2nd stage	2448	2180	1775	1766	1951	2026	2255	1719	2092	1855	2007	227	76	Rise p < 0·001
	Post partum	2095	1995	2360	2067	2103	2305	2357	2614	2331	2468	2269	188	59	Rise p < 0·05

Plasma unconjugated E_3 and hPL were measured by radioimmunoassay using kits supplied by Radiochemical Centre, Amersham. Plasma SP_1 was measured using immunodiffusion plates supplied by Behring Diagnostics. Plasma 11-HOCS levels were measured by the method of Mattingley (1962). Plasma progesterone was measured by radioimmunoassay using antiserum raised against progesterone conjugated to bovine serum albumin (BSA) through C11. Progesterone was extracted with petroleum ether and the bound and free steroid separated with dextran coated charcoal. Plasma E_2 was measured by radioimmunoassay using antiserum raised against E_2 conjugated to BSA through C6. The E_2 was extracted with alkaline ether followed by carbon tetrachloride/sodium hydroxide partitioning. After incubation with antiserum bound and free steroids were separated with dextran coated charcoal.

RESULTS

The plasma levels of the several hormones measured before induction, during the first and second stages of labour and one hour post partum are shown in Table I.

All ten patients showed a progressive rise in the plasma level of unconjugated E_3 and 11-HOCS throughout labour. By one hour post partum the unconjugated E_3 had fallen to 37 per cent of its pre-induction level whereas the 11-HOCS level continued to rise after delivery and reached 264 per cent of its preinduction level by one hour post partum (Fig. 1). The mean differences at each stage were statistically significant ($p < 0{\cdot}001$).

Plasma E_2 showed an initial small rise in the first stage followed by a significant fall in the later stages of labour and then it fell rapidly to 21 per cent of its pre-induction level by one hour post partum (Fig. 1). The mean differences at each stage were significant ($p < 0{\cdot}05$).

Progesterone levels fell progressively throughout labour with a significant difference in the mean level at each stage ($p < 0{\cdot}001$), and one hour after placental separation the level had reached 23 per cent of its pre-induction value (Fig. 1).

SP_1 and hPL showed only their normal late pregnancy variability (Masson *et al*, 1977) during labour, but by one hour post partum, hPL had fallen to 15 per cent of its pre-induction level whereas SP_1 had only fallen to 85 per cent of its pre-induction level (Fig. 1).

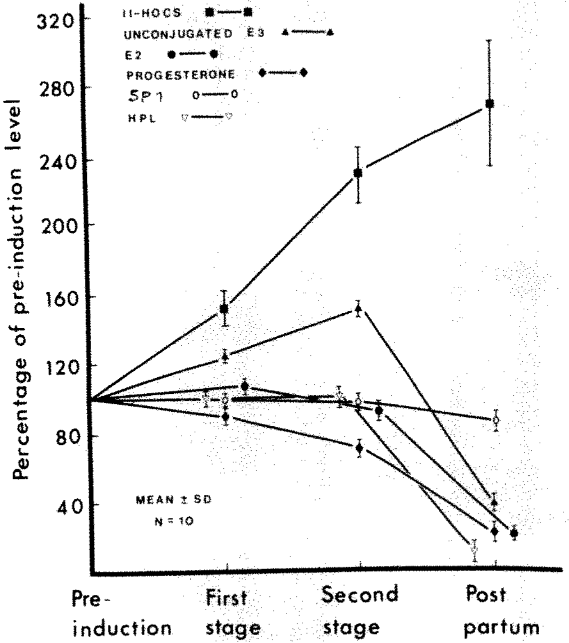

FIG. 1

Plasma levels of the six hormones measured before induction, during the first and second stages on labour and one hour post partum.

The mean P:E_2 ratio before induction of labour was 7·0:1 (range 6·3:1 to 8·5:1) during the first stage of labour the P:E_2 ratio fell to 6·2:1 (range 4·9:1 to 7·0:1) and in the second stage of labour the P:E_2 ratio fell still further to 5·4:1 (range 4·3:1 to 7·9:1).

DISCUSSION

By comparing the changes in the plasma level of placental hormones during labour with the postpartum decline resulting from the complete cessation of production with the removal of the placenta, hormone production during labour may be studied. Unconjugated E_3, E_2, progesterone and hPL all have half-lives of less than 30 minutes (Klopper *et al*, 1978; Tulchinsky and Korenman, 1971; Fylling, 1970), and any alteration in production rate will be rapidly reflected in the plasma level. SP_1, however, with a half-life of 22 hours (Klopper *et al*, 1978) will

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MATERNAL HORMONE PROFILE IN OXYTOCIN INDUCED LABOUR

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Summary

Serial blood samples were collected from ten patients at between 40 and 42 weeks gestation, who were having labour induced by amniotomy and intravenous oxytocin. The plasma levels of human placental lactogen and pregnancy-specific β_1 glycoprotein showed no more than their normal late pregnancy variability during labour; oestradiol-17β showed a small rise in early labour followed by a fall in the second stage of labour; unconjugated oestriol and 11-hydroxycorticosteroids showed a progressive rise throughout labour and progesterone a progressive fall. The ratio of progesterone to oestradiol-17β fell throughout labour. The significance of these changes in our understanding of the control of placental hormone secretion and of the hormone profile of spontaneous labour is discussed.

THERE is a considerable amount of evidence to suggest that steroid hormones may play a role in the initiation and control of labour. Liggins (1973) has put forward a theory concerning the integrated interaction of fetal and placental hormones in the onset of labour. His theory, supported by studies in the sheep and goat, suggests that a rise in fetal cortisol production leads to an increase in oestradiol-17β (E_2) and a fall in progesterone production by the placenta. These changes increase myometrial sensitivity to oxytocin by causing release of prostaglandins from the uterine decidua. The reduction of the progesterone:oestradiol-17β ($P:E_2$) ratio as a prerequisite for spontaneous labour has been postulated for many years (Csapo, 1961; Turnbull *et al*, 1974). However, studies have failed to show any consistent change in maternal oestrogens (Shaaban and Klopper, 1973), progesterone (Ances *et al*, 1971; Yannone *et al*, 1968) or cortisol (Lefebure *et al*, 1970) before the onset of spontaneous labour in humans.

This study was designed to examine the effect of induction of labour by amniotomy and intravenous oxytocin on the plasma levels of progesterone, E_2, unconjugated oestriol (E_3), human placental lactogen (hPL), pregnancy-specific β_1 glycoprotein (Schwangerscháftsproteine 1 or SP_1) and 11-hydroxycorticosteroids (11-HOCS) before, during and after labour.

PATIENTS AND METHODS

Ten healthy, fully informed, volunteer patients who were having labour induced by amniotomy and intravenous oxytocin, because they were at between 40 and 42 weeks gestation, were selected. In all patients labour was uncomplicated, delivery was spontaneous and analgesia was provided by intramuscular pethidine when required. All the infants delivered were healthy, of normal birth weight and had Apgar scores at one minute of more than 7.

Blood was taken by venepuncture before induction of labour, once the cervix was at least 5 cm dilated, in the second stage and one hour after delivery. The separated plasmas were stored at −20°C until assayed.

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and a further three-fold by the gestation of 40 weeks. In the present study there was little evidence of squalene in the amniotic fluid pellet for pregnancies less than 39 weeks in duration. The large increase in squalene content appeared to occur between the gestations of 39 to 40 weeks. In this regard the pattern of squalene accumulation is rather similar to that of the Nile Blue sulphate-staining cells which occurs between the gestations of 38 and 40 weeks (Brosens and Gordon, 1966). The appearance of squalene and of fat cells in amniotic fluid may be linked to the disappearance of the barrier posed by the *vernix caseosa* as has been suggested by Huisjes (1970). Since squalene is predominantly sebaceous in origin (Nicolaides and Rothman, 1955) the maturation of sebaceous glands could be another factor. Triglycerides are believed to be derived both from epidermal cells and from sebaceous glands (Greene *et al*, 1970).

A number of lipids in amniotic fluid which are used as indices of fetal maturity are found in much higher concentration in maternal plasma. This is the case for triglycerides, lecithin and sphingomyelin. The contamination of amniotic fluid by maternal blood, therefore, makes interpretation of data on lipids difficult. Squalene, however, is an exception in that it is found in term amniotic fluid in much higher concentration than in maternal plasma. We have measured a mean squalene concentration of 0·23 μmol/l in plasma from five pregnant women compared to 9·9 μmol/l in the term amniotic fluid pellet. Ten ml of term amniotic fluid contains 99 nmol of squalene in the pellet to which only 0·23 nmol of squalene is further contributed by each ml of maternal plasma. On these grounds it becomes apparent that the squalene content in the amniotic fluid pellet from term pregnancies can be used as an index of fetal maturity in heavily blood-stained samples. We have found maternal urine to contain even less squalene than maternal plasma.

Since there is evidence of a greater incidence of fetal morbidity and a doubling of fetal mortality in prolonged pregnancies (Zwerdling, 1967; Beischer *et al*, 1969), a test indicating that a pregnancy is several weeks overdue would be valuable in management of such pregnancies. From our study it appeared that a squalene content of greater than 20 μmol/l in the amniotic fluid pellet was indicative of a prolonged pregnancy.

The data presented here is preliminary in nature because of the small number of patients in the series. In addition, pregnancies in which altered hormone levels could have an effect on skin lipids in amniotic fluid were not available for study. With these reservations in mind we feel that the determination of the S/C ratio and squalene in amniotic fluid should be considered in normal pregnancies where the clinician needs an additional index of fetal maturity in deciding whether a pregnancy has reached term.

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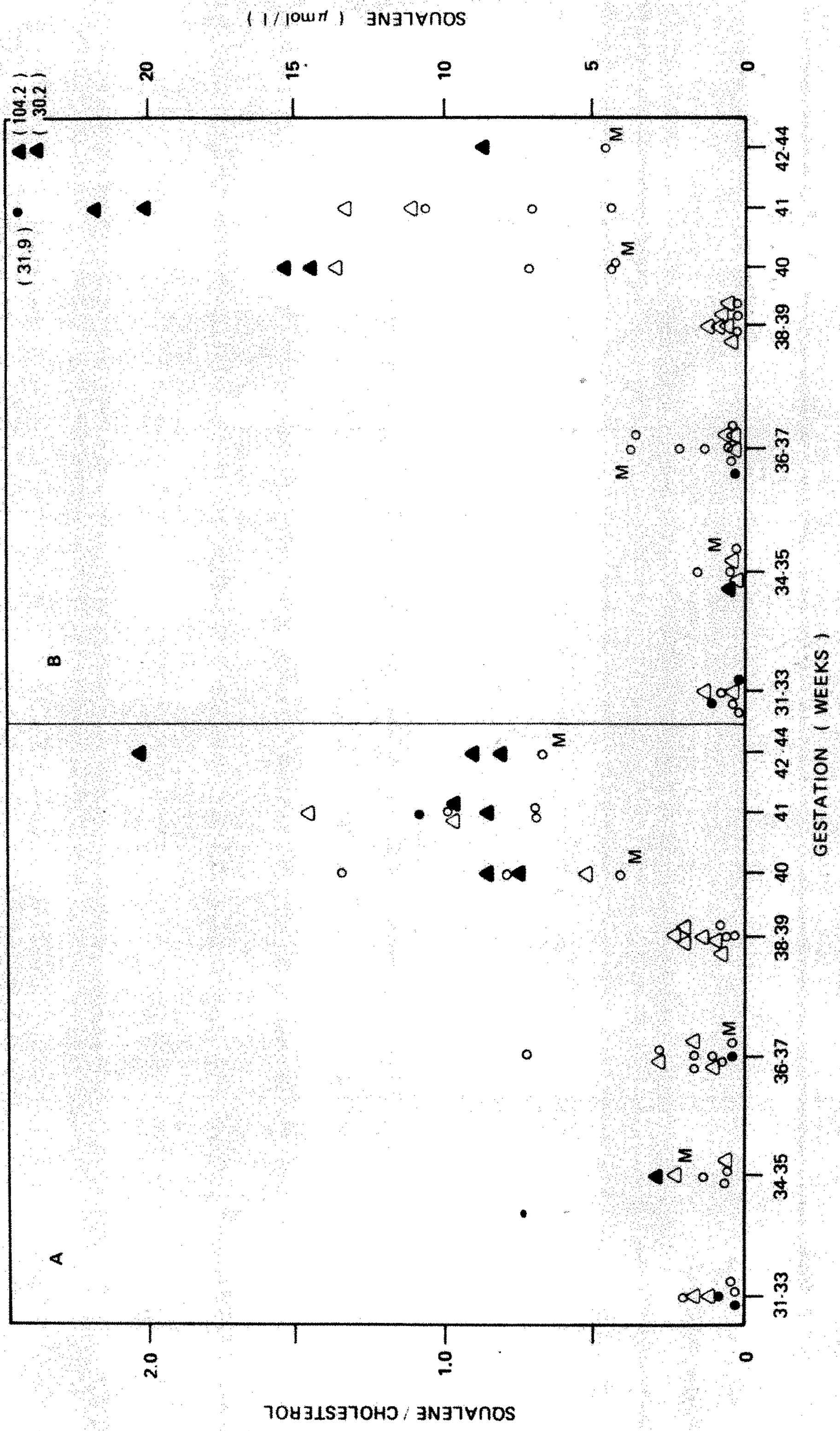

FIG. 2

Squalene content and the ratio of squalene to cholesterol in amniotic fluid pellets from patients during pregnancy. △, male fetus; ○, female fetus. ▲, ●, blood stained samples. M, meconium-stained sample.

RESULTS

The direct injection of total lipid extracts onto a short non-polar column results in resolution of neutral lipids into different classes on the basis of molecular weight. Profiles obtained in this way for pellets prepared from amniotic fluid collected at 38 weeks gestation, at term and at 44 weeks gestation are shown in Figure 1. The identities of peaks labelled squalene and cholesterol were confirmed by gas chromatography-mass spectrometry. Other peaks were assigned identity on the basis of retention data and co-chromatography with standards. The most striking difference between the profiles was the presence of substantial amounts of squalene in the term sample and its increased prominence in the post-term sample. The pattern of squalene accumulation reported here parallels that of the fat cells in amniotic fluid as described by Brosens and Gordon (1966); in other words both events occur after the 38th week of pregnancy. Peaks designated as wax esters and triglycerides were also increased in term samples in contrast to cholesterol which remained a relatively constant feature of the profiles.

It became apparent that squalene concentration in the amniotic fluid pellet by itself, or expressed as a ratio relative to cholesterol, could be an indication of the gestational age of the fetus in the last weeks of pregnancy. Data compiled from analyses on 51 specimens is shown in Figure 2. Values greater than 0·4 for squalene/cholesterol (S/C, mol/mol) or 4 μmol for squalene in the pellet from a litre of amniotic fluid were highly predictive that the pregnancy was of a gestation of 40 weeks. The difference between values for samples collected at gestations of less than 40 weeks and those at gestations of 40 weeks or later was very significant ($p<0 \cdot 001$, unpaired Student's 't' test), for both the S/C ratio and for squalene.

The concentration of squalene in amniotic fluid pellets tended to increase in pregnancies that continued beyond term. Mean values for squalene were 9·9 μmol/l at a gestation of 40 weeks, 15·0 μmol/l at 41 weeks and 36·9 μmol/l at 42 to 44 weeks. Values of greater than 20 μmol/l were obtained for five pregnancies of gestations of 41 weeks or later, clearly outside the range of values for pregnancies of a gestation of 40 weeks. However, values for seven other prolonged pregnancies could not be separated from those for pregnancies of 40 weeks duration. In one pregnancy that went to 44 weeks the S/C ratio was 2·0 and the squalene was 104 μmol/l. The finding of greatly elevated squalenes in pregnancies of such duration could not be repeated in this study as this was the only pregnancy allowed to continue beyond 42 weeks.

Samples of term amniotic fluid which were blood-stained could still be distinguished from samples collected at earlier gestations both on the basis of the S/C ratio and the squalene concentration in pellets. An amniotic fluid specimen which was heavily contaminated by meconium had an unusually large cholesterol peak in the gas chromatogram indicating the presence of cholesterol or related steroids in meconium. Three other amniotic fluids which were slightly contaminated by meconium had results which were expected for the gestations at which they were collected.

There was no relation between the S/C ratio and squalene in amniotic fluid pellets and the birth weight of the baby.

DISCUSSION

A biochemical test indicating that a pregnancy has reached term is often needed in the management of high-risk patients. It had been hoped that amniotic fluid creatinine would provide such information (Pitkin and Zwirek, 1967) but later experience showed that the test is an unreliable index of fetal maturity (Foulds and Pennock, 1972). The histochemical quantitation of fat cells by the Nile Blue sulphate-staining procedure of Brosens and Gordon (1966) is imprecise and open to misinterpretation. The ratio of lecithin to sphingomyelin in amniotic fluid gives a valuable index of fetal lung maturity (Gluck *et al*, 1971) but correlates well with gestational age only in normal pregnancies (Singh *et al*, 1974). Both in normal and abnormal pregnancies, increased accuracy in estimating gestation late in pregnancy is obtained by using a combination of procedures (Perkins, 1974).

The glyceride content in the amniotic fluid pellet was correlated with gestation in the last two months of pregnancy in a study by Gambert *et al* (1976). These authors reported that the glyceride/protein ratio in the pellet increased seven-fold between the gestations 32 to 38 weeks otic fluid volumes in pregnancies on squalene values.

The identities of peaks designated as cholesterol and squalene were verified by gas chromatography—mass spectrometry. The gas chromatograph was fitted with a glass column (6 feet × 2 mm ID) packed with 3 per cent SE-30 on chromosorb W AW-DCMS and coupled to a Varian MAT 311 mass spectrometer. The flow rate of helium was 30 ml/minute and the temperature program was 200° to 320°C at 4°/minute.

The reproducibility of squalene analysis was investigated by taking $10 \times 1{\cdot}0$ ml aliquots of a pooled pellet homogenate through the method. The data obtained was squalene $5{\cdot}91 \pm 0{\cdot}14$ (mean ± SD), CV 2·36 per cent; S/C ratio $0{\cdot}87 \pm 0{\cdot}042$, CV 4·85 per cent.

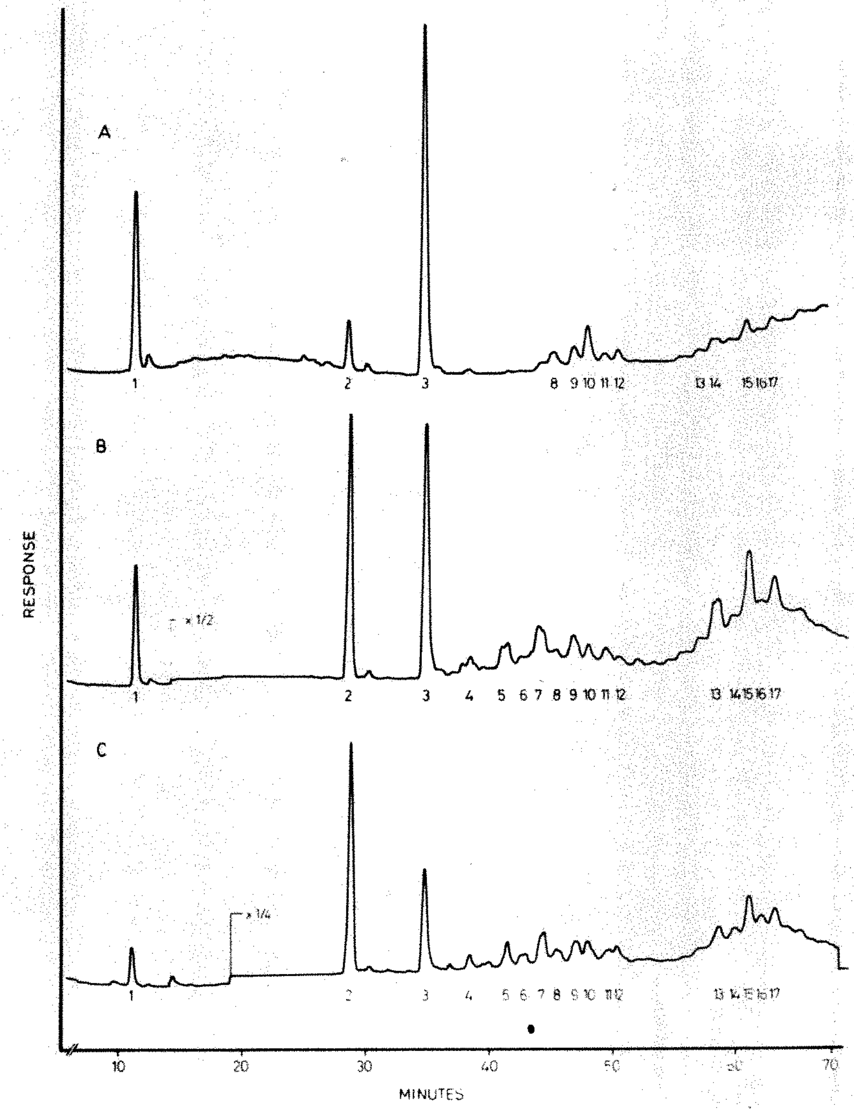

FIG. 1

Gas chromatograms of neutral lipids in washed pellets from amniotic fluid. Patient's gestations were A, 38 weeks; B, 40 weeks; C, 44 weeks. Peaks were identified as: 1, n-eicosane (internal standard); 2, squalene; 3, cholesterol; 4–7, wax esters; 8–12, diglycerides; 13 and 14, cholesteroyl esters; 15–17, triglycerides.

glands (Nicolaides and Rothman, 1955; Nicolaides *et al*, 1968). In this preliminary study, data are presented showing the usefulness of analysis of squalene in an amniotic fluid pellet in the assessment of fetal maturity in pregnancies near term.

METHODS

Chemicals

Squalene, n-eicosane and 2,6-di-t-butyl-p-cresol were products of Sigma Chemical Co, St Louis, Missouri. Squalene (2,6,10,15,19,23-hexamethyl-tetracosane) was supplied by Koch-Light Laboratories, Colnbrook, Bucks, England. Hanks balanced salt solution was purchased from the Commonwealth Serum Laboratories Melbourne, Australia. Ethyl-acetate from BDH Chemicals (Australia) Port Fairy, Victoria, was freshly distilled. Other solvents were of analytical reagent grade and were purchased from BDH Chemicals (Australia).

Amniotic fluid specimens

Amniotic fluid was collected by transabdominal amniocentesis for fetal maturity studies and prior to Caesarean section. Some specimens of amniotic fluid were obtained transvaginally during labour using a Drew-Smythe catheter. All samples were immediately centrifuged, the pellets were washed as described below and frozen at −20°C until processed.

Assessment of gestation

The gestations of patients were calculated from the date of the last menstrual period, taking into account the certainty of dates. Ultrasound was performed on all patients where there was a discrepancy between fundal size and dates. Babies were also examined within three days of birth using the Parkin test (Parkin *et al*, 1976) as an additional assessment of gestational age.

Lipid extraction

The preparation of amniotic fluid supernatant and a pellet containing amniotic cells and debris was as described by Gambert *et al* (1976). Care was taken to minimise contamination of the pellet by material floating on the surfaces of the supernatant and the salt solution wash. This was done by a combination of careful aspiration and of wiping of the interior of the centrifuge tube with a tissue.

Extraction of non-polar lipids in the amniotic fluid pellet was by a modification of a method described by Slayback *et al* (1977). The pellet was resuspended in 1·0 ml of distilled water in a culture tube with a Teflon-lined screw cap and mixed with 1·0 ml of acetone containing an anti-oxidant, 2,6-di-t-butyl-p-cresol, at a concentration of 0·005 per cent. The mixture was then vortexed for 45 seconds and 2·0 ml of ethylacetate was added. An aliquot of a standard solution of n-eicosane or squalene equivalent to 10 μg was added at this stage. After vortexing for a further 45 seconds, the tube was centrifuged at 850 *g* for 5 minutes. The upper phase was carefully transferred to a small reaction vial and evaporated to dryness under a stream of nitrogen. To aid in evaporation the vial was immersed in a water bath at 37°C. The residue was redissolved in 50 μl of petroleum ether (BP 40 to 60°C) immediately before injection into the gas chromatograph. Care was taken to maintain a nitrogen atmosphere in tubes and vials at all steps in the extraction procedure. Where residues had to be stored for any length of time, tubes were wrapped in aluminium foil and refrigerated at 4°C. The extraction procedure was verified by taking standard solutions of squalene and cholesterol through the method and both lipids were found to be quantitatively recovered (100 ± 2 per cent).

Gas chromatography

A portion (1 to 5 μl) of the extract was chromatographed on a short glass column (18 inches × 2 mm ID) packed with 3 per cent Dexsil 400 on Supelcoport 100 and fitted in a Varian 2740 gas chromatograph. The flow rate of helium was 60 ml/minute and the temperature program was from 100° to 350°C at 4°/minute. Areas of peaks were calculated by triangulation. There were slight differences in relative detector responses for compounds (relative weight responses 0·95, 1·06, 1·00 for cholesterol, squalene and n-eicosane respectively) and these were taken into account in calculations. Results were expressed as the ratio of squalene to cholesterol, that is a lipid changing in concentration in the amniotic fluid pellet to one relatively constant in the pellet, to allow for the influence of variability of amni-

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AMNIOTIC FLUID SQUALENE AND FETAL MATURITY

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Summary

Gas chromatographic profiles of neutral lipids in amniotic fluid pellets were analysed for 51 specimens collected from patients in the last two months of pregnancy. The most noticeable change was a large increase in squalene relative to other components in samples at term. By expressing data as a ratio of squalene to cholesterol (S/C), it was possible to accurately predict which amniotic fluid specimens came from patients whose pregnancies were of a gestation of 40 weeks or later. Highest values for S/C and for squalene were obtained for pregnancies which were several weeks overdue.

The possibility that amniotic fluid lipids could be correlated with fetal development was first systematically investigated by Biezenski *et al* (1968). These authors found that lipid profiles of amniotic fluid from normal pregnancies at different gestations were highly characteristic and reproducible. The concentrations of hydrocarbons in amniotic fluid and sediment were commented on since they were only found in such large amounts in one other tissue, namely skin. More detailed analysis of hydrocarbons to be found in term amniotic fluid was the subject of a study by Singh and Zuspan (1973). The most prominent of the hydrocarbons was found to be squalene which ranged from 72 to 78 per cent of the total hydrocarbons. Both of these investigations presented grouped data or data on amniotic fluid collected during labour.

Since then, relatively little attention has been paid to changes in neutral lipids of amniotic fluid in the last few weeks of pregnancy despite the well-known observation that Nile Blue sulphate-staining cells, rich in neutral lipid, accumulate in amniotic fluid just before term (Brosens and Gordon, 1966). Recently, Gambert *et al* (1976) published data showing a large increase in glycerides of amniotic cells in pregnancies approaching term. These glycerides presumably originated from the fetal skin surface, skin lipids being rich in triglycerides and also in squalene which is made by sebaceous

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differing incidences reported; 1 in 1445 (Abdul-Karim and Iskandar, 1962), 1 in 3600 (Buckingham *et al*, 1960), 1 in 12 500 (Mueller, 1948) and 1 in 14 383 (Queenan and Gadow, 1970), and much of the confusion surrounding the associations of acute polyhydramnios. Macafee (1950) reported an incidence of 1 in 6010, and stated that all the cases he observed were associated with monozygous twins.

The differential diagnoses of acute polyamnios (Pritchard and McDonald, 1976) include ovarian cysts, a rapidly enlarging hydatidiform mole and ascites. In our experience these conditions did not produce significant diagnostic problems, but difficulty did arise in distinguishing between acute polyhydramnios and concealed placental abruption. Two patients were encountered who presented with a history of rapid uterine enlargement in the second trimester associated with gross uterine distension and discomfort. Initially both were diagnosed as having acute polyhydramnios but at delivery large retroplacental haematomas were found without evidence of polyhydramnios. O'Driscoll (1945) described a similar patient and quoted others in which these conditions were confused. We feel that placental abruption should be recognized as an important differential diagnosis, and that the differentiating features are that in acute polyhydramnios the duration of symptoms is usually longer, the abdominal enlargement is greater and the radiographic and ultrasonographic features of twins and polyhydramnios are distinctive.

The remarkable feature in our series was the invariable association of acute polyhydramnios with monozygous twin pregnancy. The incidence of acute polyhydramnios complicating twin pregnancies was 1 in 53·5 (2 per cent). Although no other figures are available for direct comparison, this incidence is similar to that of 1 in 73 which may be derived from the figures quoted by Macafee (1950). Although several authors have noted some association between acute polyhydramnios and monozygous twins (Mueller, 1948; Macafee, 1950; Abdul-Karim and Iskandar, 1962; Mueller and Decker, 1963) and many individual examples have been described (Erskine, 1944; O'Driscoll, 1945; Danziger, 1948; Brown, 1958) the extent of this relationship has not been fully appreciated.

The aetiology of acute polyhydramnios remains unknown (Pritchard and McDonald, 1976). The observations that acute polyhydramnios is always associated with monozygous twins and only occurs in a limited period, between 21 and 28 weeks of gestation, suggests that there is a fetoplacental circulatory development at this stage that can result in polyhydramnios. This indicates that vascular connections between the two fetoplacental circulations may be the key to the pathogenesis of acute polyhydramnios.

Acute polyhydramnios is associated with normal infants which contrasts with the high incidence of fetal abnormalities found with chronic polyhydramnios (Macafee, 1950). The exception in our series was patient No. 4 in whom both infants were found to be Campomelic dwarfs but as this association appears to be unique it is of doubtful significance. The fetal prognosis associated with acute polyhydramnios is poor and in our series the mortality was 100 per cent. This mortality rate is in general agreement with others although individual reports exist of the survival of one infant and death of the other *in utero* (Erskine, 1944; Danziger, 1948; Brown, 1958).

As acute polyhydramnios has a high fetal mortality rate and is a significant contributor to perinatal loss in twin gestation (14·9 per cent) it is important to consider the possibilities of successful management. Although conservative management may be attempted it is usually unsuccessful and in our series six of the pregnancies terminated spontaneously. Amniocentesis has been used successfully (Erskine, 1944; Danziger, 1948; Brown, 1958), its aim being to alleviate maternal symptoms and to prevent premature labour or rupture of the membranes long enough to allow spontaneous resolution following the death of one of the infants. However, conservative management is not without maternal risk and in two patients in our series (Table II, No. 1 and 8) it had to be abandoned because of imminent maternal cardiorespiratory collapse which was associated with amniocentesis in one patient (No. 8). In our series, seven of the infants had birth weights greater than 600 g indicating that appropriate arrangements should be made for delivery and neonatal resuscitation in all cases of acute polyhydramnios.

hydramnios. Clinically all patients presented with gross uterine distension, the fundal height being equivalent to 38 to 40 weeks of gestation, and was often associated with moderate or severe uterine pain which frequently required narcotic analgesia. Associated symptoms were varying degrees of upper abdominal discomfort, dyspnoea and marked abdominal, vulval and dependant oedema. The clinical course of acute polyhydramnios was fulminant, the mean duration being eight days (range 3 to 16 days). No antenatal amniotic fluid volume studies were undertaken but the volume was measured as accurately as possible at rupture of the membranes or delivery in 5 of the 8 patients and was found to range from 4 to 10 litres (Table II). Measurements were not possible in the remaining three patients as the membranes ruptured in unfavourable situations but the volume was described as gross in all these patients. In none of the six patients with diamniotic sacs did the polyhydramnios complicate both sacs and in patients No. 6 and 7 it was specifically recorded as present only in the amniotic sac associated with the larger twin.

None of the 16 infants survived: 8 were stillborn and 8 died in the neonatal period. Birth weights ranged from 190 to 1180 g. Although fetal mortality due to acute polyhydramnios accounted for only 1·8 per cent (16 of 887) of the total perinatal mortality in this hospital during the eight-year period reviewed, it represented a very significant cause of fetal loss in twin pregnancy, namely 16 of 107 or 14·9 per cent (Table III). The contribution to the early loss in twin pregnancy (before 30 weeks of gestation) was even more significant, constituting 21·0 per cent. Congenital abnormalities were not associated with acute polyhydramnios apart from patient No. 4. This patient presented at 24 weeks of gestation with a history of acute polyhydramnios for two weeks associated with moderate uterine pain, marked general discomfort and oedema. Premature labour rapidly supervened and the patient was delivered of stillborn male monozygous twins who showed the features of the Campomelic syndrome (Storer and Grossman, 1974) with disturbances of bone growth affecting the spine, femora, humeri and tibiae.

DISCUSSION

Our experience indicated that acute polyhydramnios occurs in the second trimester, has a precipitate course usually resulting in termination of the pregnancy within a few days, and is associated with monozygous twins which are usually normal. We feel that this is a distinctly separate entity from other forms of polyhydramnios.

Clinically the diagnosis of polyhydramnios does not usually present any great difficulty, the major problem being one of classification into acute, subacute and chronic. As this classification is subjective, the term acute polyhydramnios has been used differently by many authors, some having taken the severity of the maternal symptoms rather than the rate of accumulation of the amniotic fluid as their selective criterion (O'Driscoll, 1945). The term acute polyhydramnios denotes the rapid accumulation of excessive amniotic fluid and this alone should be the diagnostic criterion and ideally should be based on objective measurement of the rate of increase either by dye dilution techniques or by ultrasonography. These variations in interpretation have resulted in the widely

TABLE III

The contribution of acute polyhydramnios to the overall fetal loss and to the loss before 30 weeks gestation in twin pregnancies

	Twin pregnancies	Twin pregnancies before 30 weeks gestation
Fetal loss	107	76
Fetal loss due to acute polyhydramnios	16	16
Proportion due to acute polyhydramnios (per cent)	14·9	21·0

hydramnios was acceptable in only eight, an incidence of 1 in 3888 pregnancies. Of the four patients excluded, two were misdiagnoses in which twin pregnancies were complicated by concealed placental abruption without evidence of polyhydramnios at delivery. The remaining two patients had undoubted polyhydramnios and one had episodes of severe abdominal pain, but premature labour only occurred after 34 and 42 days respectively and so both diagnoses were changed to subacute polyhydramnios.

All eight patients with acute polyhydramnios had monozygotic twins (Table I), an incidence of acute polyhydramnios complicating twin pregnancy of 1 in 53·5 (2 per cent). The zygosity was established histologically in all except patient No. 5 in whom the placenta and membranes were described macroscopically as diamniotic and monochorionic. No relation (Table I) was noted between the occurrence of acute polyhydramnios and fetal sex, birth weight, abnormalities or mode of death.

The basic clinical details of each patient are given in Table II. Acute polyhydramnios was not related to age or parity and there was no relevant past history, particularly of poly-

TABLE I

Details of the infants affected by acute polyhydramnios

Patient No.	Twin I			Twin II			Fetal abnormality	Membranes	Zygosity
	Sex	Weight (g)	Outcome	Sex	Weight (g)	Outcome			
1	M	190	NND (3 minutes)	M	270	NND (1 hour)	None	MM	Monozygous
2	M	450	SB	M	330	SB	None	DM	Monozygous
3	F	745	NND (1·5 hours)	F	590	SB	None	DM	Monozygous
4	M	500	SB	M	410	SB	Campomelic syndrome	MM	Monozygous
5	F	550	SB	F	710	SB	None	DM	Monozygous
6	F	710	SB	F	780	NND (30 minutes)	None	DM	Monozygous
7	M	880	NND (1·3 hours)	M	580	NND (2 days)	None	DM	Monozygous
8	F	1180	NND (7 days)	F	910	NND (4 days)	None	DM	Monozygous

M = Male
F = Female
SB = Stillbirth
NND = Neonatal death
DM = Diamniotic monochorionic
MM = Monoamniotic monochorionic

TABLE II

Clinical details of eight patients with acute polyhydramnios

Patient No.	Age (years)	Parity	Gestation at delivery (weeks)	Duration of symptoms (days)	Fundal height (weeks)	Amniotic fluid volume (ml)	Outcome
1	23	1	21	5	34	Gross	POL
2	34	1	24	3	40	10 000	PROM
3	22	0	24	14	38	Gross	POL
4	34	1	24	16	40	4000	POL
5	25	0	25	4	38	Gross	PROM
6	27	1	25	10	38	5000	PROM
7	31	1	27	9	40	4000	ARM
8	26	2	28	3	40	8000	ARM

ARM = Artificial rupture of the membranes.
PROM = Premature rupture of the membranes.
POL = Premature onset of labour.

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ACUTE POLYHYDRAMNIOS— A COMPLICATION OF MONOZYGOUS TWIN PREGNANCY

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Summary

Eight patients with acute polyhydramnios were encountered in 31 103 pregnancies, an incidence of 1 in 3888. All patients with acute polyhydramnios had monozygous twin pregnancies and 14 of the 16 infants were normal. The condition occurred in the second trimester and usually ended in premature delivery within a few days. The perinatal mortality was 100 per cent and accounted for 14·9 per cent of the perinatal mortality in twins.

ACUTE polyhydramnios is an uncommon complication of pregnancy characterized by a rapid increase in amniotic fluid volume resulting in immense uterine distension within a few days and producing severe discomfort and pressure symptoms. Due to its rarity there is little collected experience of the condition and this is reflected in the sparse and rather confused literature on the subject. There is little agreement on its incidence, its associations with multiple and/or singleton pregnancies or with fetal abnormalities, the fetal mortality and the possibility of successful management.

This paper represents a review of the experience of acute polyhydramnios at one maternity hospital, its associations and the perinatal outcome.

METHODS

The case notes of all patients with polyhydramnios who were admitted to the Mercy Maternity Hospital, Melbourne, during the eight years 1971 to 1978 were reviewed. The patients were classified into those with acute, subacute and chronic polyhydramnios on the basis of documentary evidence of the amniotic fluid volume, the rate of development of the polyhydramnios and the severity of the symptoms produced. In an attempt to minimize the subjective nature of this classification the dominant criterion was the rate of development of the polyhydramnios.

The zygosity of the twin pregnancies was established from the description of the placenta and membranes and confirmed where possible by histological examination of the membranes (Corney, 1975).

RESULTS

During the eight years reviewed, 31 103 pregnancies greater than 20 weeks of gestation were managed at the Mercy Maternity Hospital, of which 428 were twin pregnancies. On examination of the case records, polyhydramnios was diagnosed in 250 patients (0·8 per cent) of which 12 were classified as having acute polyhydramnios. When these 12 patients were critically reviewed the diagnosis of acute poly-

TABLE III

Relationship of placental site at early pregnancy ultrasound examination to abnormalities of pregnancy

	Placental site	
Pregnancy abnormality	Low (n = 175)	Other (n = 440)
Small-for-dates infant*	16†	12†
Pre-eclampsia	11	19
Premature labour	3	9
Fetal distress in labour	5	7
Placenta praevia	5	0
Antepartum haemorrhage without placenta praevia	5	4

* Less than 10th percentile for gestational age based on Flinders Medical Centre data for a normal obstetric population.

† $p < 0{\cdot}005$.

confirmed at examination under anaesthesia. In the remaining patient, a Caesarean section was done for other reasons and the low placental site was confirmed at operation.

It is now clear that an apparently 'low lying' placenta in early pregnancy must be considered as an anatomical variant (King, 1973; Wexler and Gottesfeld, 1977). The apparent 'migration' of the placenta to the upper segment (King, 1973) may be due to technical inexperience or to inadequate bladder distension preventing satisfactory outlining of the cervix and lower uterus. However, placental location can change in relation to external landmarks due to changes in uterine position. More importantly, progressive uterine enlargement brings about a change in placental site in relation to internal uterine landmarks. Thus with the formation of the lower uterine segment there is a relatively dramatic movement of the lower margin of the upper uterine segment away from the internal cervical os and this tends to carry the margin of an initially 'low lying' placenta away from the lower uterine segment. Thus an ultrasound diagnosis of placenta praevia in an otherwise normal patient should not be made before 34 weeks.

We found an association between 'low lying' placenta in early pregnancy and a 'small-for-dates' infant. Perhaps implantation in the lower part of the uterus provides inadequate conditions for normal placental growth and perfusion. Varma (1973) strengthened this possibility by finding a 22 per cent incidence of fetal growth retardation in 150 patients with placenta praevia but in her series, all patients had experienced antepartum haemorrhage and there was a correlation between fetal growth and the number of episodes of bleeding. Like Wexler and Gottesfeld (1977), we found no other pregnancy abnormalities associated with a 'low lying' placenta.

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TABLE I

Placental site in early pregnancy related to fetal biparietal diameter (BPD) in 615 patients

Fetal BPD (cm)	No. of patients	Placental site			
		Low	Anterior	Posterior	Fundal
≦4·0	174	56 (32%)	46 (27%)	58 (33%)	14 8%)
4·1–5·0	323	97 (30%)	98 (30%)	107 (33%)	22 (7%)
5·1–6·0	118	21 (18%)	39 (33%)	49 (41%)	9 (8%)
Total	615	174 (28%)	183 (30%)	214 (35%)	45 7%)

BPD standards for Flinders Medical Centre:

4·0 cm = 18 weeks
5·0 cm = 21 weeks
6·0 cm = 24 weeks

was synonymous with placenta praevia indicating a placenta encroaching on the lower uterine segment.

The medical records of all patients were reviewed to determine pregnancy outcome which was correlated with placental site in early gestation.

RESULTS

Table I shows the placental location found in 615 patients on routine ultrasound screening prior to 24 weeks gestation. A total of 174 patients were found to have a 'low lying' placenta. The results were related to fetal biparietal diameter (BPD) but may be translated to fetal maturity by referring to the footnote of Table I. Table II shows the progressive decrease in incidence of 'low lying' placenta with advancing pregnancy in 94 women whose ultrasound examination was repeated. Table III relates placental site determined by initial ultrasound examination to pregnancy outcome in the total group of 615 patients. There was an apparent association of 'low lying' placenta with small-for-dates babies but not with the other pregnancy abnormalities analysed.

DISCUSSION

A 'low lying' placenta was present in 28 per cent of patients studied by ultrasound at less than 24 weeks. Within this group there was a progressive decrease of 'low lying' placenta from the earliest to the latest gestation groups and this decline continued with the advance of pregnancy. In the group of 94 patients with a 'low lying' placenta before 24 weeks who were scanned again in later pregnancy, the placenta was located in the upper uterine segment in all but five. These were the only five patients with placenta praevia in the total group of 174 patients with a 'low lying' placenta at the first ultrasound examination. Of the five, two patients had an antepartum haemorrhage and were delivered by Caesarean section. In a further two patients the diagnosis of placenta praevia was

TABLE II

Incidence of subsequent low placental site in 94 women who were re-scanned later in pregnancy related to fetal BPD

Fetal BPD (cm)	Patients	
	No.	Per cent*
≦7·0	94	100
7·1–8·0	34	36·0
8·1–9·0	20	22·1
>9·0	5	5·3

* The initial group of 94 = 100 per cent.

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SIGNIFICANCE OF THE ULTRASOUND LOCATION OF PLACENTAL SITE IN EARLY PREGNANCY

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Summary

The placenta was located by routine ultrasound scanning before 24 weeks gestation in 615 consecutive obstetric patients. A 'low lying' placenta was present in 175 (28 per cent) of the total group; the incidence decreasing from 32 per cent at 16 weeks gestation to 18 per cent at 24 weeks. Of 94 women with an initial 'low lying' placenta who were selected for rescanning, only five had a placenta praevia persisting beyond the 34th week. Patients with an early 'low lying' placenta had a significantly higher incidence of small-for-dates babies than those in whom the placenta remained clear of the internal cervical os on ultrasound scanning.

ROUTINE ultrasound examination of the uterine contents in the first half of pregnancy has been proposed as an aid to obstetric management (Bradley-Watson and Mitchell, 1973; Williams *et al*, 1977). The placental site can be determined at this time and a study was undertaken to determine the anatomical and clinical significance of a 'low lying' placenta in early pregnancy.

PATIENTS AND METHODS

Routine ultrasound scanning in the second trimester of pregnancy is done on all patients attending the obstetric clinics at the Flinders Medical Centre, Adelaide, using a Unirad GZD Model 849 Scanner. A routine procedure is employed with particular emphasis on adequate bladder distension. The present study involved 615 consecutive patients screened at less than 24 weeks gestation. Of a total of 174 patients with an initial 'low lying' placenta, 94 were re-examined later in pregnancy either for specific clinical indications unrelated to placental site or because the early pregnancy ultrasound demonstrated a 'low lying' placenta of significant degree. The follow-up group were therefore selected.

Placental site at the initial examination was classified as either low or normal, the latter being further subdivided into anterior, posterior and fundal. A low placenta was defined as one extending to or covering the internal cervical os. Clearly there was a risk of subjective bias in the assessment of minor degrees of 'low lying' placenta and this may have led to an over-diagnosis of the phenomenon. Bladder under-filling could potentially contribute to this bias. At subsequent examinations 'low lying' placenta breathing incidence and maximum breathing rate for the same time periods before and after artificial rupture of the membranes.

DISCUSSION

A significant rise in fetal breathing incidence and maximum breathing rate was observed during the first five to ten minutes after amniotomy. The mechanism which causes this short-term phenomenon is not yet understood. The incidence of FBM falls during active labour in man (Boddy and Dawes, 1975; Richardson *et al*, 1979). In the present study, however, there were no clinical signs of uterine activity and the fetal heart rate remained normal throughout. The only other study dealing with FBM and changes in the amniotic fluid compartment was published by Manning *et al* (1977). They examined the effect of amniocentesis on FBM and observed a significant fall in the incidence of FBM up to two days after the procedure.

But Manning *et al* (1977) did not study FBM immediately before and after amniocentesis. We conclude that the mechanisms responsible for the control of FBM are very sensitive to changes in fetal environment and this must be taken into account when using fetal breathing as an index of fetal well-being.

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TABLE I

Change in breathing incidence after amniotomy

Time after amniotomy (minutes)	Change in breathing incidence when compared to equivalent time span before amniotomy (per cent)								Total showing	
	0–50		51–100		101–200		> 200			
	Increase	Decrease	Increase	Decrease	Increase	Decrease	Increase	Decrease	Increase	Decrease
0–5	2	2	1	–	4	–	5	1	12	3
0–10	1	4	2	–	2	1	5	–	10	5
0–15	3	4	2	–	1	–	4	1	10	5

TABLE II

Change in maximum breathing rate after amniotomy

Time after amniotomy (minutes)	Change in maximum breathing rate when compared to equivalent time-span before amniotomy (per cent)								Total showing	
	0–50		51–100		101–200		> 200			
	Increase	Decrease	Increase	Decrease	Increase	Decrease	Increase	Decrease	Increase	Decrease
0–5	5	1	2	1	3	–	3	–	13	2
0–10	9	2	1	–	1	–	2	–	13	2
0–15	8	3	1	–	1	–	2	–	12	3

TABLE III

Values for breathing incidence before and after amniotomy

Minutes before amniotomy	Mean	SD	Minutes after amniotomy	Mean	SD	p-value
0–5	67·1	54·6	0–5	120·3	60·1	< 0·05
0–10	136·9	108·6	0–10	205·0	89·5	< 0·05
0–15	219·0	163·4	0–15	262·7	130·3	> 0·05

TABLE IV

Values for maximum breathing rate before and after amniotomy

Minutes before amniotomy	Mean	SD	Minutes after amniotomy	Mean	SD	p-value
0–5	26·8	18·9	0–5	39·3	13·5	< 0·05
0–10	32·7	18·3	0–10	42·7	13·1	< 0·05
0–15	37·1	16·7	0–15	42·9	13·2	> 0·05

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EFFECT OF AMNIOTOMY ON FETAL BREATHING MOVEMENTS

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Summary

Fetal breathing movements were recorded by real-time ultrasound before and after artificial rupture of the membranes. Fifteen normal pregnancies between 39 and 41 weeks gestation were studied. A significant increase in breathing incidence and maximum breathing rate was observed in the first 10 minutes after amniotomy.

REAL-TIME and Doppler ultrasound system allow detailed studies of fetal breathing movements (FBM) in man (Boyce *et al*, 1976; Wladimiroff *et al*, 1976; Marsal *et al*, 1978). FBM are influenced by maternal gaseous exchange (Wladimiroff *et al*, 1977), blood glucose levels (Fox and Hohler, 1977; Patrick *et al*, 1978), exercise (Marsal *et al*, 1976) and cigarette smoking (Gennser *et al*, 1975). In this study FBM were assessed before and after amniotomy.

MATERIAL AND METHODS

Fifteen normal patients giving informed consent were included in the study; the gestational age was 40 to 42 weeks in 14 patients and 39 weeks in one patient. All patients had labour induced by rupture of the forewaters at 0900 hours. During this procedure, all amniotic fluid was drained off and its volume measured. All patients were in the supine position during the study period. No medication or cigarette smoking was allowed from the evening before induction. A multielement dynamically focussing ultrasound transducer (Ligtvoet *et al*, 1977) was used and FBM were observed on the monitor and plotted on a magnetic tape by means of an event marker. From this were calculated: breathing incidence, namely the total number of FBM over a study period of five minutes, and maximum breathing rate, namely the maximum number of FBM observed per minute over a study period of five minutes. Observations were made over a period of 15 minutes before and 15 minutes after artificial rupture of the membranes. Fetal heart rate was measured every five minutes by means of a fetal stethoscope.

RESULTS

During the entire observation period, there were no uterine contractions. Clear amniotic fluid was obtained from all patients and the volume of amniotic fluid withdrawn ranged from 300 to 900 ml. The fetal heart rates varied between 125 to 160 beats/minute.

Tables I and II show the percentage change in breathing incidence and maximum breathing rate in the 15 minutes (or portions thereof) after amniotomy as compared to the 15 minutes (or portions thereof) before. Tables III and IV give the mean values and standard deviations for

Alternatively the relationship may be due to an unknown factor which causes increased antepartum fetal activity and abnormal fetal heart rate in labour.

The high fetal movement counts recorded by mothers taking sedatives or tranquillizers may be related to either maternal personality traits (such as anxiety which is transmitted to the fetus), the direct effects of the drugs on the fetus, or increased perception of fetal movement by the mother.

The unusually high fetal movement counts in the fetus with a true knot in the umbilical cord suggest either that a very active baby may become entangled with the cord, or that accidental entanglement leads to increased fetal movement. The former explanation seems more likely as the baby was quite healthy at birth.

It was unfortunate that the two mothers who had asphyxiated babies at birth stopped counting fetal movements one or more days before delivery. The number of mothers counting movements declined over the last seven days before delivery (Fig. 1 to 3) and this tendency may be a problem in the clinical use of subjective fetal movement counts. The absence of movements on four consecutive occasions was not a useful indication of fetal condition. Nevertheless, this does not negate the claim of Sadovsky *et al* (1978) that the absence of fetal movement over a 12-hour period is an indication of fetal ill health, as the patients in the present study did not count movements for this length of time. It does indicate a possible defect in our endeavour to establish adequate methods for subjective recording. The following suggestion may resolve this. If the mother fails to record fetal movements on three consecutive occasions, which involves 8 per cent of the present 'high-risk' population, then she could be asked to count movements over the succeeding 12-hour period. In our previous study we found that women could not count fetal movements accurately over a 12-hour period. Nevertheless, if movements are absent during two consecutive 20-minute periods, patients may be more motivated to check for the presence of *any* movement whatsoever in a 12-hour period. Another difficulty occurred in checking the usefulness of fetal movements as an antenatal test of fetal condition. Although all 'high-risk' patients were included over a period of two years, no stillbirth occurred. In view of the strength of the claims made by Sadovsky *et al* (1978) it is important that studies be undertaken in obstetric populations where a significant number of stillbirths can be expected.

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TABLE VI

Obstetrical outcome in relation to the absence of fetal movement during four consecutive periods

	Low urinary oestriol	Hypertension	Fetal growth retardation	Premature	Apgar score under 6
Fetal movement absent during 4 consecutive periods (n = 9)	2	3	2	1	1
Remainder of study group (n = 124)	10	32	8	9	9

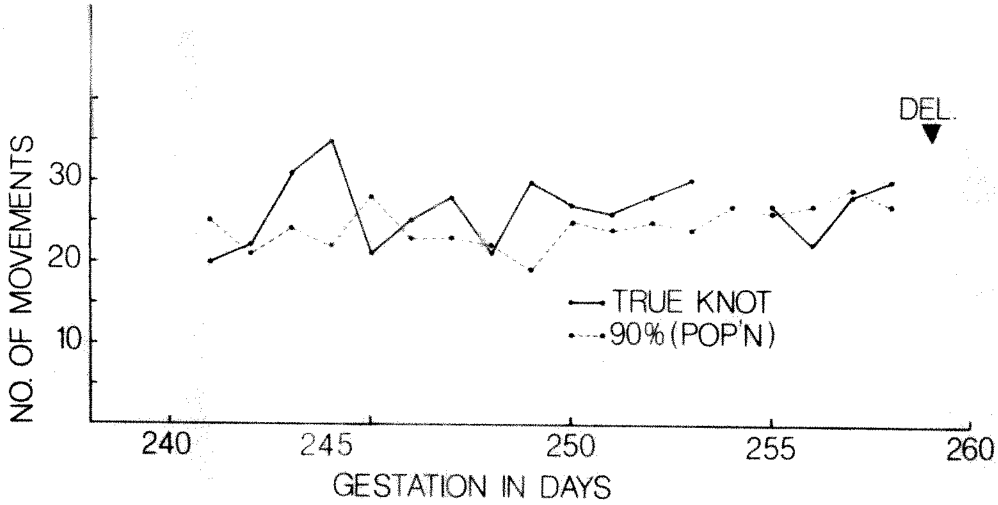

FIG. 5

Number of fetal movements counted in morning session versus day of gestation in patient with true knot in the umbilical cord.

DISCUSSION

The reduction in fetal movement counts during the later weeks of pregnancy is unlikely to be due to flagging of patients' interest in counting with elapse of time, as the change was independent of the number of days the patient was in the study. Diminished fetal activity may occur as a result of the reduction of amniotic fluid as pregnancy progresses, the fetus being cramped and less able or inclined to move. Median fetal movement counts were halved when pregnancy was prolonged beyond 42 weeks, and this information may help confirm the diagnosis of prolonged pregnancy. It is not known whether the reduction of fetal movement results from a coincident reduction of amniotic fluid or whether fetal activity is reduced because of change in the fetal nervous system.

The reduction in fetal movement amongst mothers who smoke is consistent with the finding of reduced fetal respiratory movements in such women detected by ultrasound techniques (Manning *et al*, 1975). Whether this is due to a depressant effect of nicotine on the fetal central nervous system, an increase in maternal carboxyhaemoglobin or other toxic effects of cigarette smoke is not known.

The association of high fetal movement counts with abnormal fetal heart rate during labour was unexpected. An analysis of the type of abnormal fetal heart rate showed tachycardia was present in 15 of 39 cases. Transient acceleration of the fetal heart rate is associated with fetal movement and this may explain the coincidence of abnormal fetal heart rate and increased antepartum fetal movement counts.

TABLE IV

Factors associated with fetal movement counts

Factor	No. of patients	No. of observations	Fetal movement counts 90th centile	50th centile	10th centile
Smokers	34	410	24	6	0
Non-smokers	97	1146	26	8	1
				P<0·01*	
Gestational age (weeks)					
<36	5	46	14	9	1
37–41	121	1456	26	8	1
42	11	113	12	3	0
				P<0·001†	
Infant birth weight (g)					
2001–2500	6	82	18	7	1
2501–3000	24	292	24	6	0
3001–3500	53	660	25	8	1
3501–4000	38	418	25	8	1
over 4001	14	165	24	9	2
				P = 0·02†	
Drugs used					
Sedatives/tranquillizers	7	99	26	10	2
None	9	106	19	6	0
				P<0·001*	
Others	121	1412	25	9	1
Monitored FHR					
Normal	49	582	24	6	0
Abnormal	39	398	30	9	0
				P<0·002*	

Where the total no. of patients in each group is less than 137, the relevant data were lost or not recorded.
* Wilcoxon's Rank Sum Test.
† Kruksal-Wallis Test.

TABLE V

Absence of fetal movement during consecutive counting periods

Number of consecutive periods	Total	Number of patients 1 week before delivery	More than 1 week before delivery
2	19	5	16*
3	11	4	9*
4	9	5	4
5	–	–	–

* Several patients had absence of fetal movements during consecutive periods intermittently over several weeks; this explains why the total number of patients is less than the sum of patients in the last two columns.

non-smokers, the length of pregnancy, the weight of the baby, the use of antenatal drugs and the occurrence of fetal heart rate abnormalities (see Table IV, Fig. 4).

Movements were absent on two, three or four consecutive occasions in 14, 8 and 7 per cent of patients respectively (Table V). Comparison of obstetric complications and fetal outcome showed no difference between mothers with absent fetal movement on four consecutive occasions and the rest of the study population (Table VI).

One patient in whom there was a true knot in the umbilical cord had a high fetal movement count. On 12 out of 17 days the count was above the 90th centile (Fig. 5). The cord length (94 cm) was the second largest in the study.

TABLE III

Neonatal complications and fetal movement counts

Neonatal complications	Number of patients	Number of observations	Fetal movement counts		
			90th centile	50th centile	10th centile
Respiratory disease	19	262	31	8	2
Infection	1	15	13	8	5
Jaundice	18	196	24	11	2
Other	14	182	16	5	0
None	85	941	25	8	1

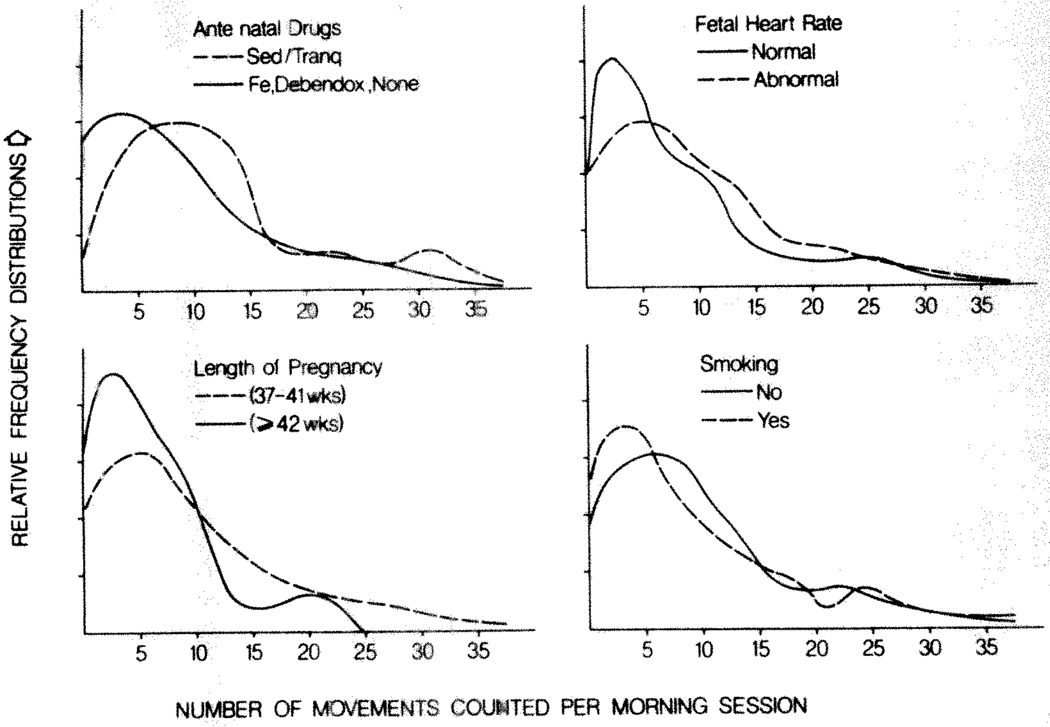

FIG. 4

Relative frequency distribution of fetal movement counts according to drug usage, fetal heart rate, duration of pregnancy and maternal smoking habit.

morbidity (Table III). While the Apgar score showed no significant correlation with fetal movement counts there were only two babies born with Apgar scores between 0 and 3 at 2 minutes after birth, the low scores being sustained at 5 minutes after birth. One of the babies died of asphyxia within 24 hours of delivery. The mother stopped counting fetal movements the day before delivery, the fetal movement counts being below the median but above the tenth centile. The other baby survived, requiring 30 minutes to establish regular respiration; the mother who had hypertension, had recorded normal fetal movement counts up to 6 days before delivery when she stopped counting. During labour severe decelerations of the fetal heart rate occurred and an emergency Caesarean section was performed.

Fetal movement counts were significantly affected by whether mothers were smokers or

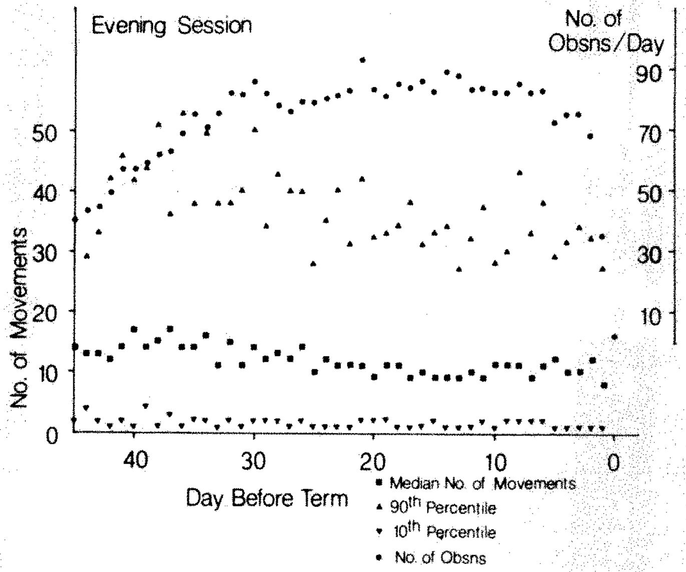

FIG. 3

Centiles for fetal movement counts made in the evening.

TABLE I

*Summary table for median sessional fetal movement counts by days before birth**

Session	Slope	Correlation coefficient	F test	Probability (p)	Degrees of freedom
Morning	−0·076	0·721	47·54	<0·01	1,44
Afternoon	−0·089	0·704	43·17	<0·01	1,44
Evening	−0·120	0·718	46·84	<0·01	1,44

* This table refers to data in Figures 1, 2 and 3.

TABLE II

Antenatal complications and fetal movement counts

			Fetal movement counts		
Antenatal complications	Number of patients	Number of observations	90th centile	50th centile	10th centile
Hypertension	17	227	28	8	0
Hypertension plus proteinuria	18	264	26	9	1
Low oestriol	12	138	20	7	2
Antepartum haemorrhage	6	83	24	8	3
Other complications	31	308	25	9	1
None	53	490	24	7	0

Statistic test was Wilcoxon's Rank test, P = ns for all antenatal complications.

stetric variables. Age, parity and ethnic origin did not influence the centile distribution of fetal movements nor did a number of antenatal complications (Table II). Other factors which did not influence fetal movement counts were the sex of the baby, the presence of congenital malformations, amniotic fluid volume, umbilical cord length, length of the baby and neonatal culated. As the mean increased so did the standard deviation and therefore centiles were used to describe the distribution of fetal movements for each day.

RESULTS

The centiles for morning, afternoon and evening counts are shown in Figures 1, 2 and 3. The morning and afternoon counts were lower than the evening counts.

The fetal movement counts decreased over the 46 days preceding birth, (Table I, Figs. 1 to 3). The morning counts were used to determine whether fetal movements were related to ob-

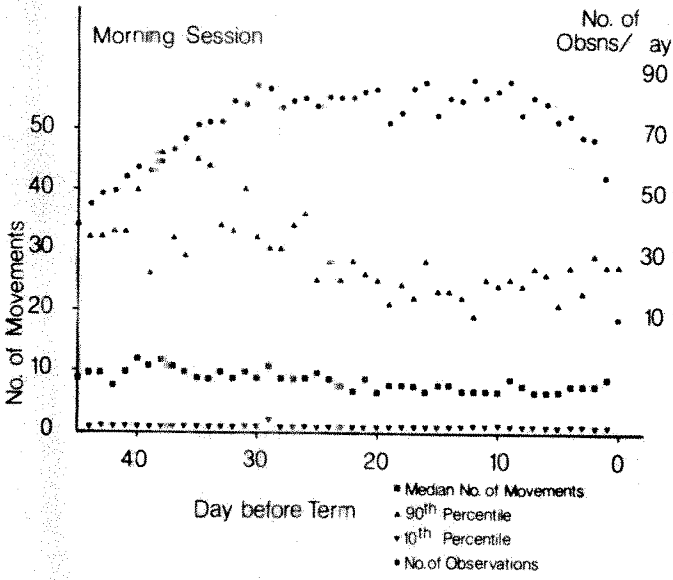

FIG. 1

Centiles for fetal movement counts made in the morning.

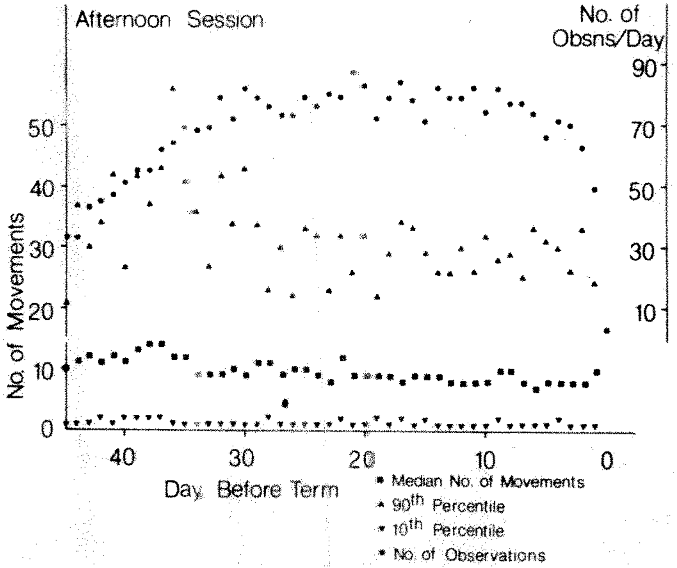

FIG. 2

Centiles for fetal movement counts made in the afternoon.

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SUBJECTIVE RECORDING OF FETAL MOVEMENT

BY

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Summary

A group of 137 patients, 113 of whom had obstetric complications, recorded fetal movements by a subjective method. Low fetal movement counts were associated with maternal cigarette smoking and prolongation of pregnancy and high counts with maternal ingestion of sedatives or tranquillizers, abnormal fetal heart rate in labour and a true knot in the umbilical cord. The absence of fetal movement during four consecutive 20-minute counting-sessions was not associated with poor fetal outcome. Further investigations to assess the usefulness of fetal movement counting are recommended. Such investigations should take into account the limitations imposed by the methods and the obstetric population for study.

SADOVSKY and Yaffe (1973) and Pearson and Weaver (1976) have shown that changes in counts of fetal movements recorded by patients can help to predict fetal death and fetal asphyxia. Indeed Sadovsky *et al* (1978) stated that a definite decrease in fetal movement counts followed by cessation of fetal movements for at least one day was an indication for prompt delivery.

Assessment of three methods of recording fetal movements showed a significant correlation between patient, observer and instrument counts when movements were recorded over 20-minute periods (Wood *et al*, 1977). Diurnal, daily and weekly variation in fetal movements occurred, the counts usually being higher in the evening, and in 3 of 9 patients significantly lower in the week before parturition. The present study was carried out to investigate movements in a larger group of patients, using the subjective method of recording developed in the previous study. In addition, fetal movement counts were correlated with several obstetric variables.

METHOD

A group of 137 patients attending the antenatal clinic of the hospital volunteered for the study. The only other criteria for the selection of patients were that they could speak English and understand the instructions for counting fetal movements. The majority of the patients had some obstetric complication in keeping with the distribution of patients attending the hospital.

The patients recorded fetal movements for three 20-minute periods each day. An instruction and recording booklet, an automatic timing device and a counter were used to enhance the accuracy of counting.

The fetal movement counts were put into a computer file and the means and standard deviations of all counts for each of the last 46 days of pregnancy before delivery were cal-chromosome mosaicism was given hormone treatment in relation to pregnancy (Mackay *et al*, 1971). She had occasional spontaneous periods between the ages of 15 and 20. At the age of 30, after cyclical oestrogen therapy, she was given three courses of clomiphene 100 mg daily for five days. Eight weeks after the last treatment she was pregnant and the pregnancy ended in the delivery of a normal female baby. The patient reported by Lieber and Berger (1973) was given cyclical oestrogen treatment from the ages of 18 to 21. At 24, after an unsuccessful attempt of culdoscopy, she began to have periods, became pregnant four months later and was granted a request for termination.

Pregnancies in women with Turner's syndrome

Fifteen out of 56 pregnancies (27 per cent) in women with Turner's syndrome aborted and there were four stillbirths, three of them associated with congenital fetal malformation. Twelve of the 37 liveborn children (32 per cent) had some physical or mental defect: 8 children (22 per cent) had abnormal karyotypes (3 had Down's syndrome; and 5 had Turner's syndrome with a 45,X cell line).

The high frequency of abortions, stillbirths and Down's syndrome could be due to premature ovarian ageing (Talbert, 1968; Reyes *et al*, 1976), but it might also reflect the fact that the birth of an abnormal fetus sometimes leads to the diagnosis of Turner's syndrome in the mother. Notwithstanding, we have no doubt about recommending prenatal fetal chromosome analysis in mothers with Turner's syndrome.

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were uncomplicated. Breast feeding lasted one month, and the first period occurred two weeks after delivery. The child was a girl (birth weight 2·98 kg; length 50 cm) without malformations and with a 46,XX karyotype and normal subsequent development.

DISCUSSION

Menstruation in women with Turner's syndrome

Singh and Carr (1966) found that the gonads of early 45,X embryos appeared to be normal, but during fetal life, at puberty, or occasionally much later, the germ cells degenerate, and typical streak gonads develop. In infants with Turner's syndrome, some workers (Frøland *et al*, 1962; Conen and Glass, 1963; Bove, 1970) have found clusters of germ cells or even primordial follicles. The total loss of germ cells and transformation of the ovaries to streak gonads may take 20 to 30 years in patients with a 46,XX or 47,XXX cell line, as well as a 45,X cell line. Our patient had her menarche at 16 and is still menstruating at the age of 20, and we have previously studied a woman with 45,X/46,XX/47,XXX mosaicism who menstruated from the ages of 16 to 34 (Nielsen and Thomsen, 1968). Thus, streak gonads are not mandatory for a diagnosis of Turner's syndrome; this was stressed by Philip and Sele (1976) who reported a patient with a 45,X karyotype who had had two pregnancies.

It is likely that only a small percentage of patients in whom a diagnosis based on an analysis of at least 50 cultured cells would have spontaneous menstruation.

Five of the seven women with a 45,X karyotype who gave birth to a total of nine children had spontaneous menstruation for a varying length of time beforehand.

The frequency of spontaneous menstruation amongst mosaics with a 46,XX or 47,XXX cell line, as well as a 45,X cell line is probably around 20 per cent as predicted by Ferguson-Smith (1965) and verified by some others (Palmer and Reichmann, 1976; Nielsen *et al*, 1977).

Conception in women with Turner's syndrome

Recent surveys by Gilboa and Rosenberg (1975), Reyes *et al* (1976), Nielsen *et al* (1977), King *et al* (1978) and Dewhurst (1978) identify nine pregnancies and six livebirths in seven women with a 45,X karyotype, but not all had thorough cytogenetic studies, and some might have had chromosomal mosaicism. However, Philip and Sele (1976) reported a patient who had two pregnancies and a 45,X chromosome constitution in all 203 cells cultured from lymphocytes, fibroblasts and ovarian tissue.

There are reports of a total of 56 pregnancies in 23 women with Turner's syndrome, 16 of whom also had 46,XX and/or 47,XXX cell lines.

It is probably very unusual for women with Turner's syndrome to give birth to a child before the age of 18 and after the age of 34. In Denmark there are approximately 600 000 women aged 18 to 34, and approximately 225 of these will have Turner's syndrome. So far, two have given birth to a child (Philip and Sele, 1976; and our patient). It is probable that about 2 per cent of women with Turner's syndrome have offspring.

Three patients have been given hormone therapy before pregnancy: the 22-year-old woman with 45,X Turner's syndrome described by Grace *et al* (1973) became pregnant after discontinuing cyclical oestrogens which she had taken for less than a year; a 20-year-old woman reported by King *et al* (1978) had cyclical oestrogen therapy from the ages of 12 to 17, then had spontaneous periods and gave birth to a normal boy at the age of 20. The patient described by Philip and Sele (1976) started cyclical oestrogen therapy at the age of 15, was found to be pregnant three months after discontinuing treatment at the age of 30, and spontaneously aborted a macerated hydrocephalic infant at about 26 weeks. She was subsequently treated unsuccessfully with gonadotrophins, then had further cyclical oestrogen therapy, became pregnant again two months after stopping oestrogens and ultimately gave birth to a normal girl. Pregnancy after oestrogen therapy has been reported in other types of hypergonadotrophic ovarian failure, namely in patients with an apparent premature menopause (Starup *et al*, 1978) or patients with the resistant ovary syndrome (Shangold *et al*, 1977). In these circumstances oestrogens may act by causing a rebound offset or by enhancing the response of the ovaries to endogenous gonadotrophins (Starup *et al*, 1978).

Only one patient with Turner's syndrome and

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FERTILITY IN WOMEN WITH TURNER'S SYNDROME CASE REPORT AND REVIEW OF LITERATURE

BY

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Summary

A successful pregnancy in a woman with Turner's syndrome with a 45,X/46,XX karyotype is described. The literature contains reports of a total of nine pregnancies in seven women with a 45,X karyotype and 56 pregnancies in 23 women with mosaicism and a 45,X cell line, as well as a 46,XX and/or 47,XXX cell line. Fifteen of the latter 56 pregnancies ended in spontaneous abortion (27 per cent), and four ended in the delivery of a stillborn child; 12 of the 37 liveborn infants (32 per cent) had a physical or mental abnormality, and 8 (22 per cent) had a chromosome abnormality. Three had Down's syndrome, and five had a 45,X cell line. Due to the relatively high (8 per cent) incidence of Down's syndrome among liveborn infants of women with Turner's syndrome, amniocentesis for fetal karyotyping should be advised.

SPONTANEOUS menstruations appear in approximately 5 per cent of women with Turner's syndrome, and some of these women give birth to children. We report a 20-year-old woman with Turner's syndrome and a 45,X/46,XX karyotype who gave birth to a child.

CASE HISTORY

The patient presented has previously been studied by Mikkelsen *et al* (1963) as one of a pair of monozygotic twins with different phenotypes and differing numbers of cells with a 45,X chromosome constitution.

The patient was one of 91 girls with Turner's syndrome found in a prevalence study among all 357 994 girls in Denmark who were between the ages of 7 and 17 on 1st September, 1973.

The patient had one normally developed elder sister, and her twin sister died at the age of 3 years (Mikkelsen *et al*, 1963). The patient developed normally, but was of short stature and, like her mother, had suffered from mild migraine since childhood.

From the age of 16 she had spontaneous and regular menstrual periods lasting 6 to 7 days and occurring every 30 days. She became pregnant at the age of 19, but did not contact a doctor until the 25th week of gestation when it was too late for amniocentesis to determine fetal karyotype. The pregnancy and delivery at term

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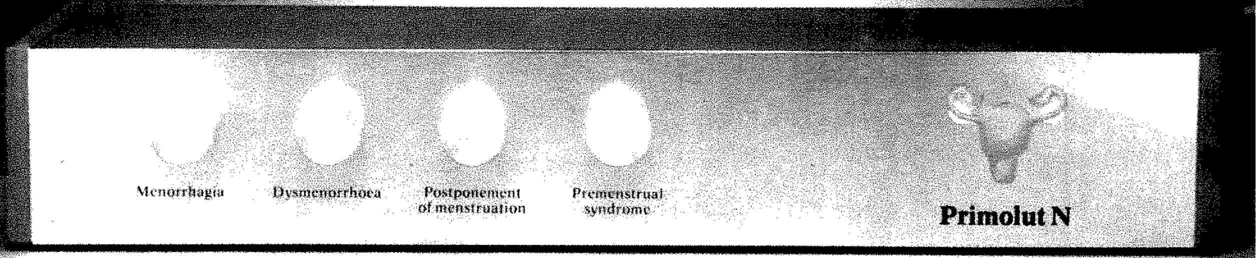

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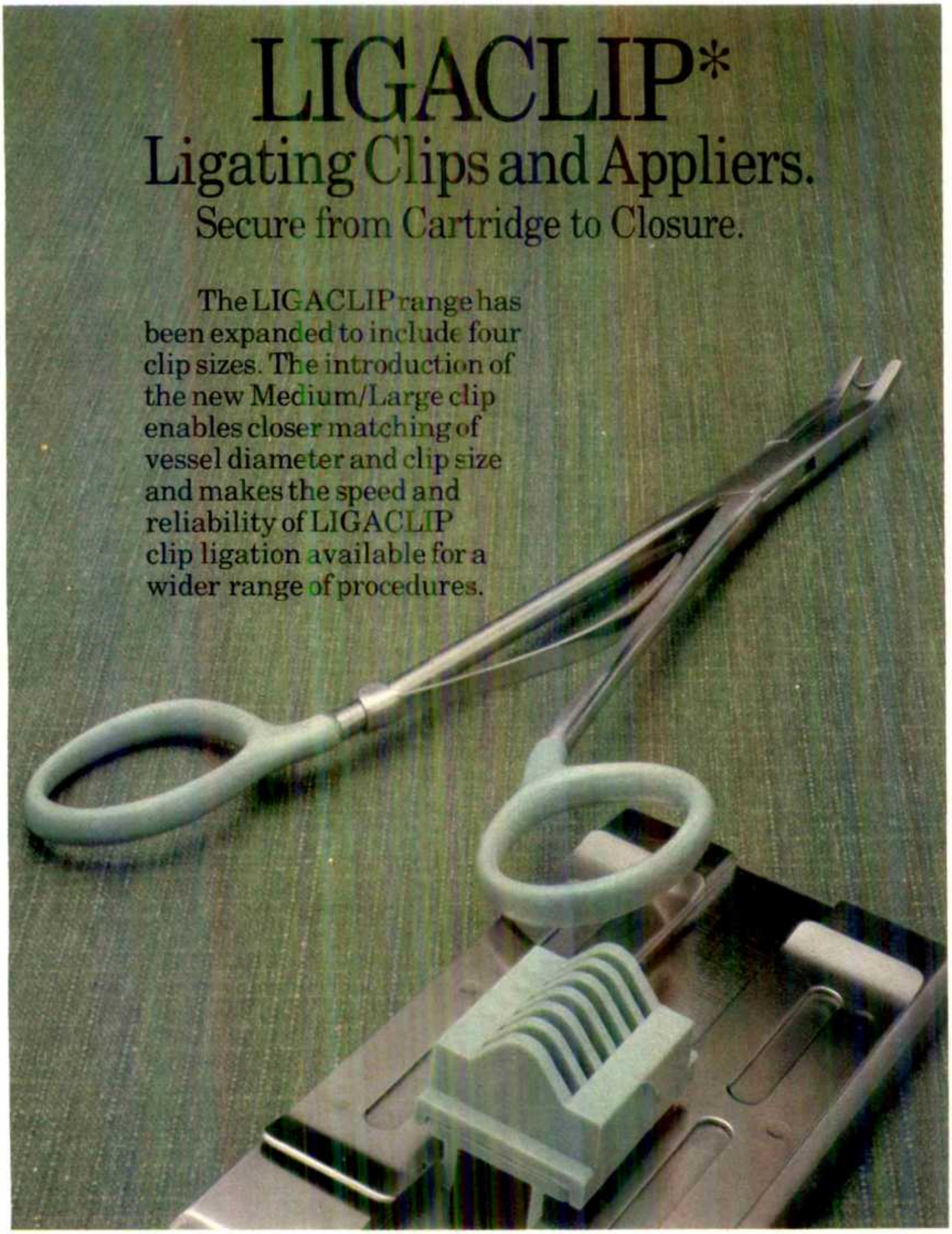

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For acute urinary tract infections 2 tablets twice daily is recommended. For long term and prophylactic therapy 1 tablet twice daily is recommended.

Contra-indications

Ipral should not be given to patients with severe renal insufficiency where blood levels cannot be monitored regularly. Ipral should not be used in pregnancy or during the first few weeks of life.

Precautions

Care is necessary in administration to patients with impaired renal function. Special precaution should be exercised in patients with a predisposition to folate deficiency.

Side-effects

Nausea, vomiting and skin rashes may occur but are rare. Ipral may depress haematopoiesis during prolonged therapy. This has proved reversible when treated with calcium folinate.

Treatment of overdosage

Gastric lavage. Calcium folinate may be used to counteract any effect of Ipral on bone-marrow.

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"Treatment with TMP (trimethoprim) alone is superior to the combined regimen due to a smaller incidence of side-effects; ..." thus "... introduction of TMP alone on the market is recommended."[4]

"Less gastrointestinal side-effects and skin rashes have occurred with trimethoprim ..."[3]

References
1. Lancet 1979, **1**, 493. 2. Br. med. J. 1972, **2**, 673.
3. Ann. clin. Res. 1978, **10**, (suppl. 22). 4. Chemother. 1973, **19**, 314.

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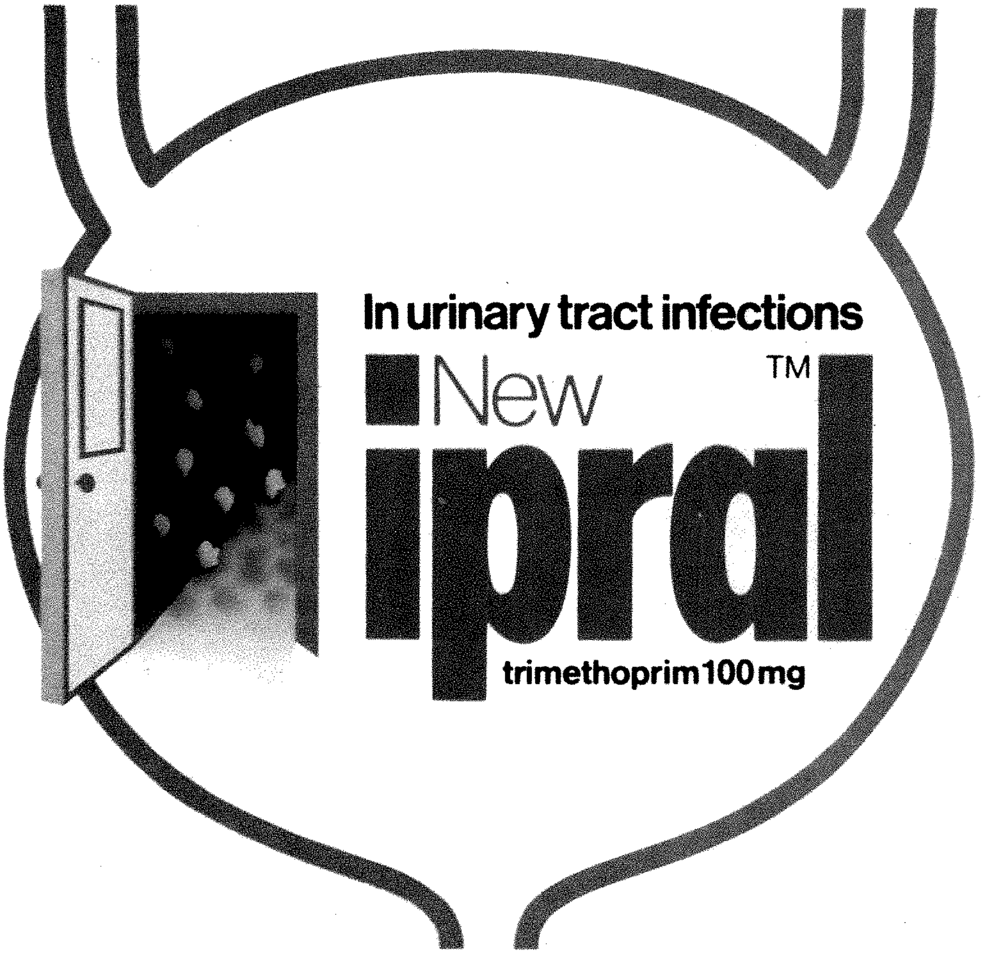

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"Trimethoprim alone may well prove as effective as trimethoprim-sulphamethoxazole combinations ..."[1]

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Antibiotic	Overall Success
Ampicillin	89%
Cephalexin	62%
Co-trimoxazole	81%
Trimethoprim	96%

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In a study on recurrent U.T.I.'s
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"... the total side effects caused by ampicillin, cephalexin and co-trimoxazole were similar and occurred twice as often as when trimethoprim was given alone ..."[2]

Antibiotic	No. of Patients	% Side Effects
Ampicillin	88	22
Cephalexin	84	25
Co-trimoxazole	83	21
Trimethoprim	**84**	**8**
Total	339	

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NEOPLATIN*

PRESENTATION

NEOPLATIN INJECTION : each vial contains 10 mg cisplatin (Cis-diamminedichloroplatinum).

USES

Cisplatin is indicated as palliative therapy to be employed in addition to other modalities, or in established combination therapy with other approved chemotherapeutic agents in the management of neoplastic diseases, especially :

Metastatic Testicular Tumours – in patients who have already received appropriate surgical and/or radiotherapeutic procedures. The combination of cisplatin, bleomycin and vinblastine has been reported to be highly effective. Other combinations have also been reported to be active.

Metastatic Ovarian Tumours – as secondary therapy in patients refractory to standard chemotherapy.

DOSAGE AND ADMINISTRATION

The recommended dose of cisplatin in adults and children as single-agent therapy is 50 to 75 mg/m^2 as a single i.v. dose every 3 to 4 weeks, or 15 to 20 mg/m^2 i.v. daily for 5 days every 3 to 4 weeks. Pre-treatment hydration with 1 to 2 litres of fluid infused for 8 to 12 hours prior to a cisplatin dose is recommended. Reconstitute vial contents with 10 ml of sterile water for Injection EP. The drug is then diluted in 2 litres of 5% dextrose in either 1/2 or 1/3 normal saline, (to which 37.5 g of mannitol may be added) and infused over a 6-8 hour period. Adequate hydration and urinary output must be maintained during the following 24 hours.

A repeat course of cisplatin should not be given until the serum creatinine is below 1.5 mg/100 ml (130 μmol/l) and/or the blood urea below 55 mg/100 ml (9 mmol/l). A repeat course should not be given until circulating blood elements are at an acceptable level (platelets 100,000/mm^3, WBC 4,000/mm^3). Subsequent doses of cisplatin should not be given until an audiometric analysis indicates that auditory acuity is within normal limits. When employed in combination with other antitumour drugs, the dose of cisplatin should be adjusted appropriately.

CONTRA-INDICATIONS, WARNINGS, ETC.

Cisplatin induces nephrotoxicity, myelosuppression and ototoxicity which may be additive to pre-existing dysfunctions. Consequently, the use of cisplatin in patients with hearing or renal impairment or depressed bone marrow function may be associated with increased toxicities. Such conditions represent relative contra-indications.

Cisplatin is contra-indicated in patients with a history of hypersensitivity to cisplatin or other platinum-containing compounds.

WARNINGS

Cisplatin produces cumulative nephrotoxicity. The serum creatinine, BUN and creatinine clearance should be measured prior to initiating therapy, and prior to each subsequent course.

Anaphylactic-like reactions to cisplatin have been reported. These reactions have occurred within minutes of administration to patients with prior exposure to cisplatin, and have been alleviated by administration of adrenaline, steroids and antihistamines.

Safe use in pregnancy has not been established. This product should not normally be administered to patients who are pregnant or to mothers who are breast feeding. Cisplatin is mutagenic in bacteria and produces chromosome aberrations in animal cells in tissue culture. Although carcinogenicity and teratogenicity have not been established, compounds with similar mechanisms of action and mutagenicity have been reported to be carcinogenic.

The influence of cisplatin on human reproduction has not been determined. Cisplatin therapy might have an antifertility effect.

Precautions

Cisplatin should be administered by individuals experienced in the use of antineoplastic therapy.

Since renal toxicity is cumulative, measurements of BUN, serum creatinine and creatinine clearance should be performed prior to initiating therapy and prior to each subsequent dose. At the recommended dosage, cisplatin should not be given more frequently than once every 3 to 4 weeks. (See Adverse Reactions).

Since ototoxicity of cisplatin is cumulative, audiometric testing should be performed prior to initiating therapy and prior to each subsequent dose of drug. (See Adverse Reactions).

Peripheral blood counts should be monitored weekly. Liver function should be monitored periodically. Neurological examination should also be performed regularly. (See Adverse Reactions).

ADVERSE REACTIONS

Nephrotoxicity

Dose-related and cumulative renal insufficiency is the major dose-limiting toxicity of cisplatin. Renal toxicity has been noted in 28 to 36% of patients treated with a single dose of 50 mg/m^2. It is first noted during the second week after a dose and is manifested by elevations in BUN and serum creatinine serum uric acid and/or a decrease in creatinine clearance.

Renal toxicity, becomes more prolonged and severe with repeated courses of the drug. Renal function must return to normal before another dose of cisplatin can be given.

Renal function impairment has been associated with renal tubular damage. The administration of cisplatin using a 6-8 hour infusion with intravenous hydration and mannitol has been used to reduce nephrotoxicity. However, renal toxicity still can occur after utilisation of these procedures.

Ototoxicity

Ototoxicity has been observed in up to 31% of patients treated with a single dose of cisplatin 50 mg/m^2, and is manifested by tinnitus and/or hearing loss in the high frequency range (4,000 to 8,000 Hz).

Decreased ability to hear normal conversational tones may occur occasionally. Ototoxic effects may be more severe in children receiving cisplatin. Hearing loss can be unilateral or bilateral and tends to become more frequent and severe with repeated doses. It is unclear whether cisplatin-induced ototoxicity is reversible. Careful monitoring of audiometry should be performed prior to initiation of therapy and prior to subsequent doses of cisplatin.

Haematological

Myelosuppression occurs in 25 to 30% of patients treated with cisplatin. The nadirs in circulating platelets and leucocytes occur between days 18 to 23 (range 7.5 to 45) with most patients recovering by day 39 (range 13 to 62). Leucopenia and thrombocytopenia are more pronounced at higher doses (50 mg/m^2). Anaemia (decrease in haemoglobin level by 2 g/100 ml blood) occurs at approximately the same frequency and with the same timing as leucopenia and thrombocytopenia.

Gastrointestinal

Marked nausea and vomiting occur in almost all patients treated with cisplatin, and are occasionally so severe that the drug must be discontinued. Nausea and vomiting usually begin within one to four hours after treatment and last up to 24 hours. Various degrees of nausea and anorexia may persist for up to one week after treatment.

OTHER TOXICITIES

Hyperuricaemia

Hyperuricaemia has been reported to occur at approximately the same frequency as the increases in BUN and serum creatinine. It is more pronounced after doses greater than 50 mg/m^2, and peak levels of uric acid generally occur between 3 to 5 days after the dose. Allopurinol therapy for hyperuricaemia effectively reduces uric acid levels.

Neurotoxicity

Neurotoxicity, usually characterised by peripheral neuropathies, has occurred in some patients. Loss of taste and seizures have also been reported.

Neuropathies resulting from cisplatin treatment may occur after prolonged therapy (4 to 7 months) ; however, neurological symptoms have been reported to occur after a single dose.

Cisplatin therapy should be discontinued when the symptoms are first observed. Preliminary evidence suggests peripheral neuropathy may be irreversible in some patients.

Anaphylactic-like Reactions

Anaphylactic-like reactions, possibly secondary to cisplatin therapy, have been occasionally reported in patients previously exposed to cisplatin. The reactions consist of facial oedema, wheezing, tachycardia and hypotension within a few minutes of drug administration. All reactions may be controlled by intravenous adrenaline, corticosteroids or antihistamines. Patients receiving cisplatin should be observed carefully for possible anaphylactic-like reactions and supportive equipment and medication should be available to treat such a complication.

Other toxicities reported to occur infrequently are cardiac abnormalities, anorexia and elevated SGOT.

PHARMACEUTICAL PRECAUTIONS

NEOPLATIN INJECTION must be stored in a refrigerator (2°C to 8°C).

EXPIRY DATE

24 months from date of manufacture.

Preparation of Intravenous Solution

Dissolve NEOPLATIN with 10 ml of sterile water for injection. Each ml of the resulting clear, colourless solution will contain 1 mg cisplatin.

The drug is diluted in 2 litres of 5% dextrose in 1/2 or 1/3 normal saline (to which 37.5 g of mannitol may be added) and given by i.v. infusion over a 6 to 8 hour period.

The reconstituted solution should be protected from light, kept at room temperature and is stable for 20 hours. Refrigeration will result in precipitation.

LEGAL CATEGORY

POM.

NEOPLATIN is available only on prescription and supplied to centres with experience in the chemotherapy of malignant disease.

PACKAGE QUANTITIES

NEOPLATIN INJECTION is packed in cartons of 10 vials, each vial containing 10 mg lyophilised cis-diamminedichloroplatinum.

FURTHER INFORMATION

Cisplatin has biochemical properties similar to that of bifunctional alkylating agents producing interstrand and intrastrand crosslinks in DNA. It is apparently cell-cycle non-specific. Following a single i.v. dose, cisplatin concentrates in liver, kidneys and large and small intestines in animals and humans. Cisplatin apparently has poor penetration into the CNS.

Plasma levels of radioactivity decay in a biphasic manner after an i.v. bolus dose of radioactive cisplatin to patients. The initial plasma half-life is 25 to 49 minutes, and the post-distribution plasma half-life is 58 to 73 hours. During the post-distribution phase, greater than 90% of the radioactivity in the blood is protein bound. Cisplatin is excreted primarily in the urine. However, urinary excretion is incomplete with only 27 to 43% of the radioactivity being excreted within the first 5 days post-dose in human beings. There are insufficient data to determine whether biliary or intestinal excretion occurs.

BASIC N.H.S. COST 10mg vial £10.75

PRODUCT LICENCE NUMBER 0125/0109

DATE OF PREPARATION

January 1979

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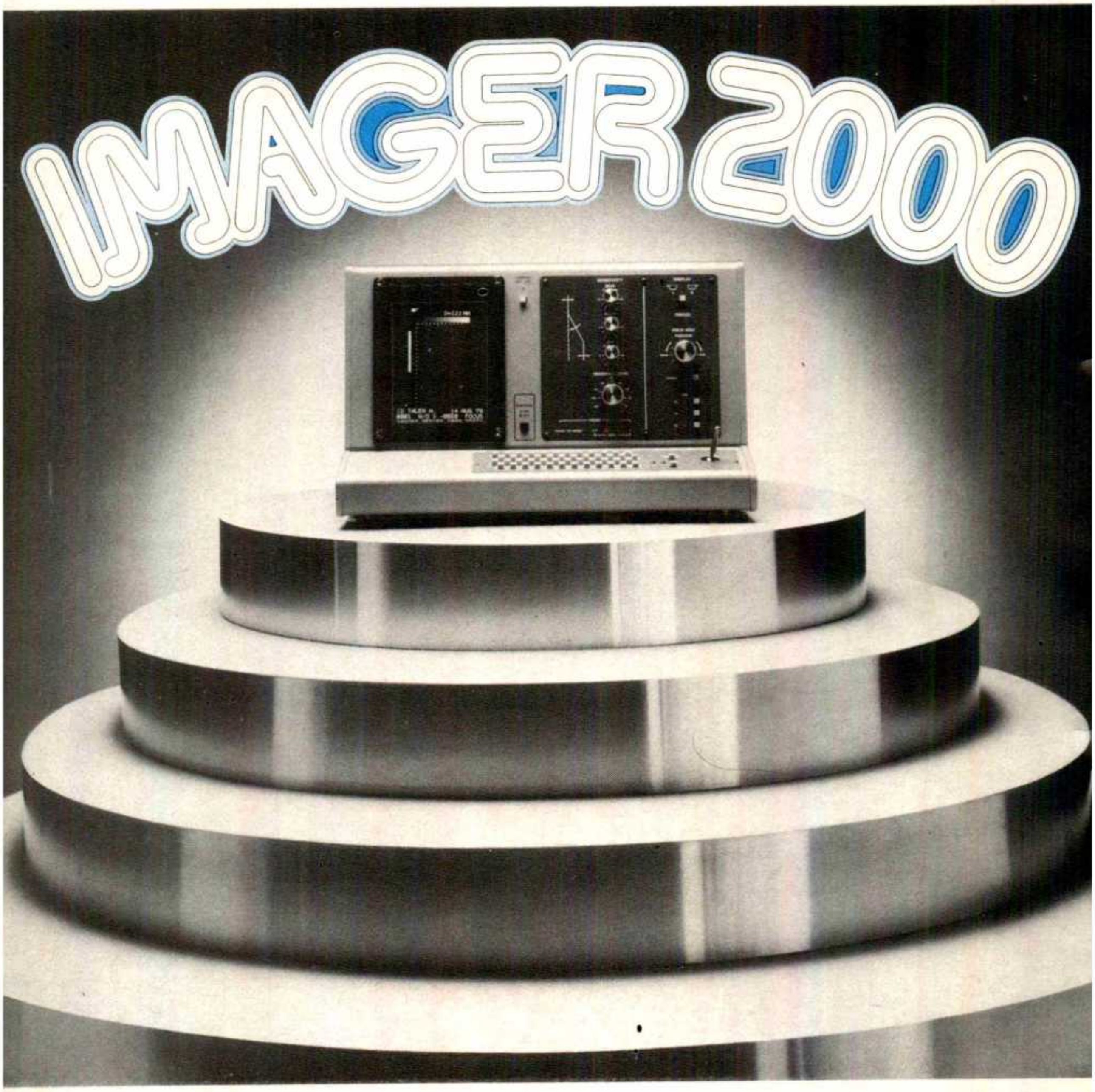

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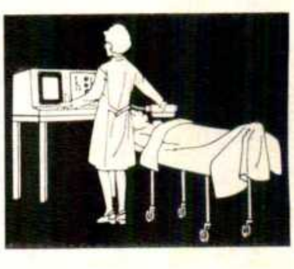

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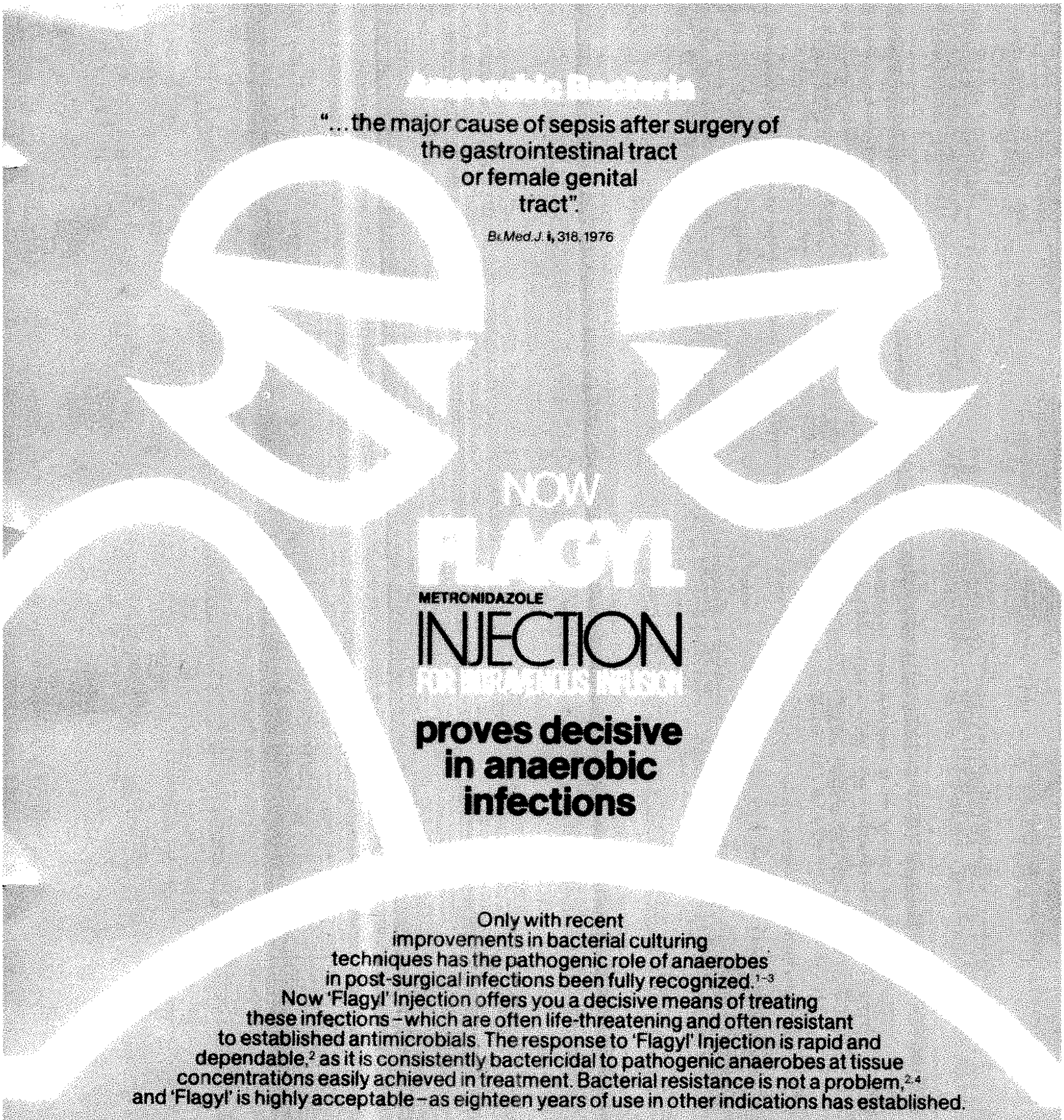

Anaerobic Bacteria

"…the major cause of sepsis after surgery of
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Br.Med.J. **i**, 318, 1976

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Basic N.H.S. cost **(as at May 1979)**
Injection for i.v. infusion Bottle of 100 ml £6.40.

References 1. Willis, A.T. (1977) Scottish Medical Journal, **22**, 155. 2. Willis, A.T. et al (1977) British Medical Journal, **i**, 607. 3. Finegold, S.M. Anaerobic Bacteria in Human Disease, Academic Press Inc. New York, 1977. 4. Willis, A.T. et al (1975) Journal of Antimicrobial Chemotherapy, **1**, 393, 1975.

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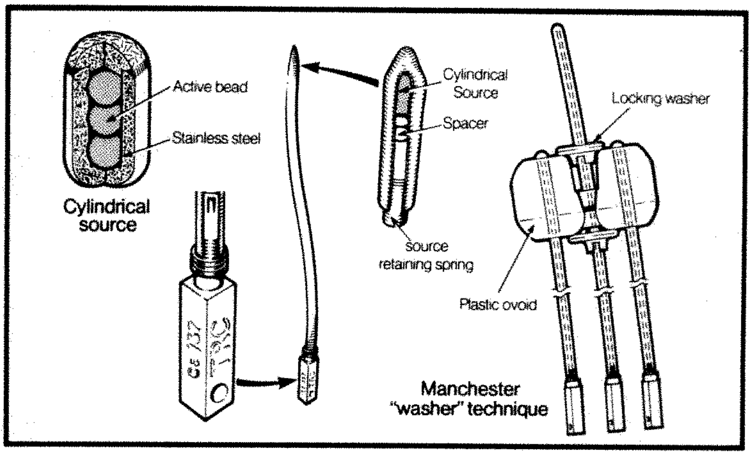

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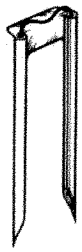

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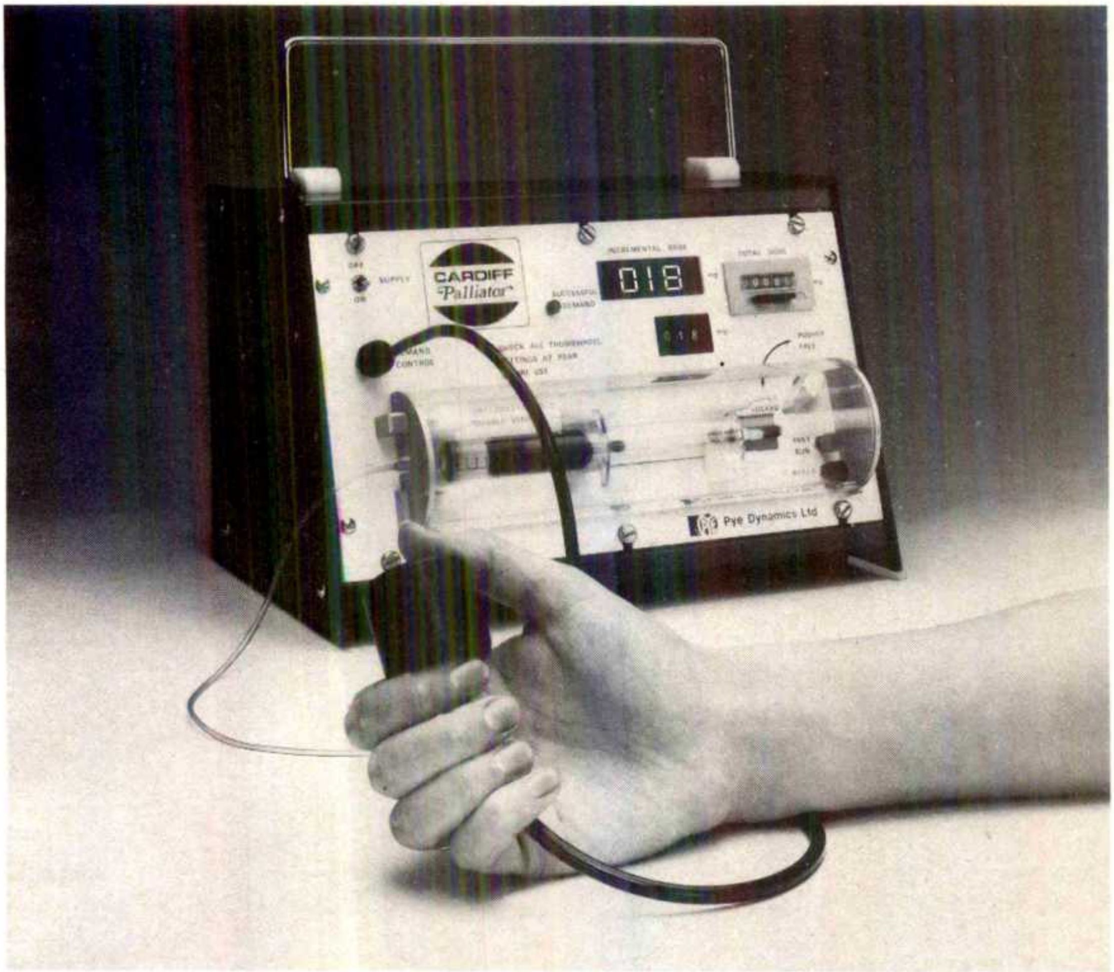

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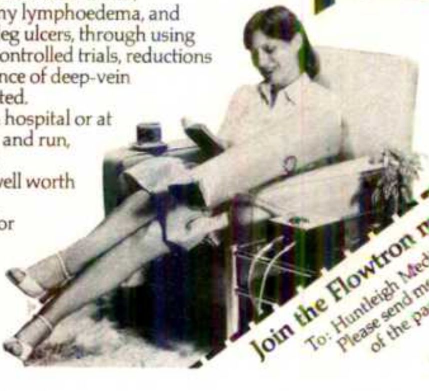

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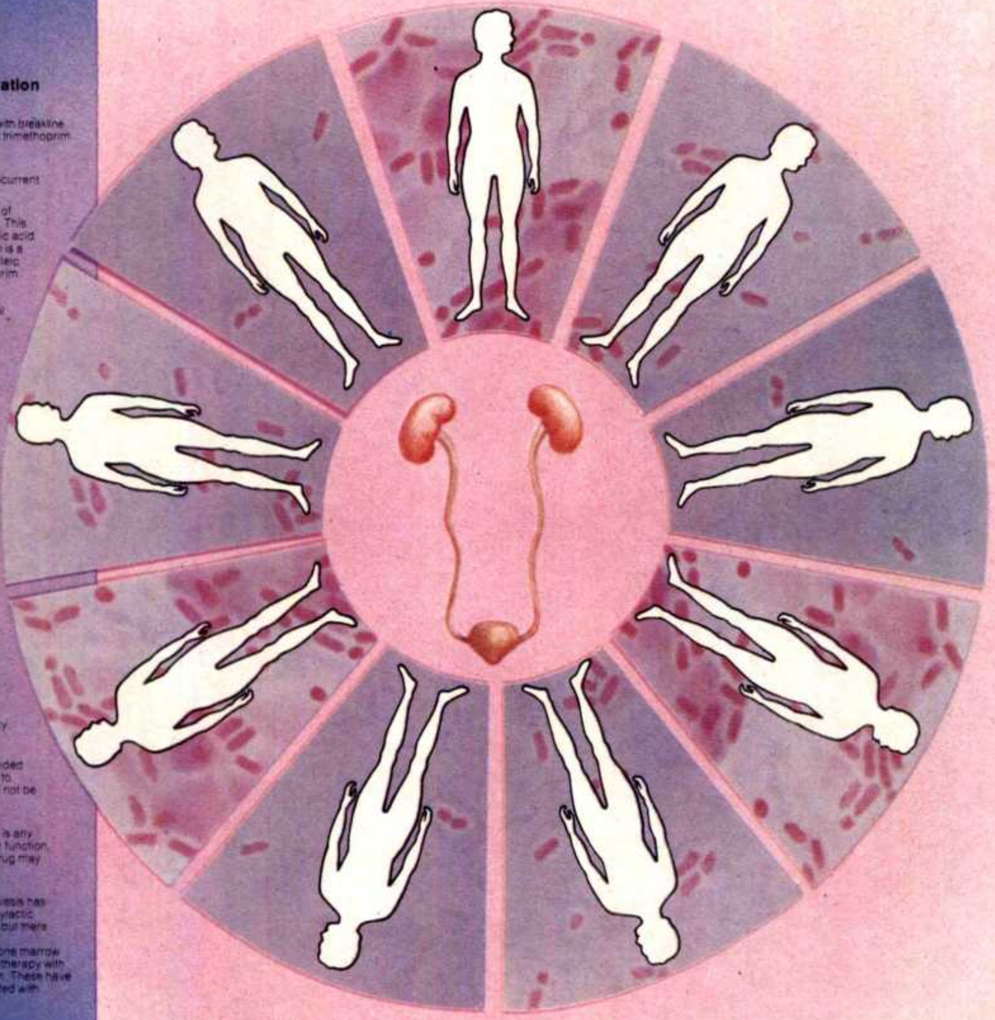

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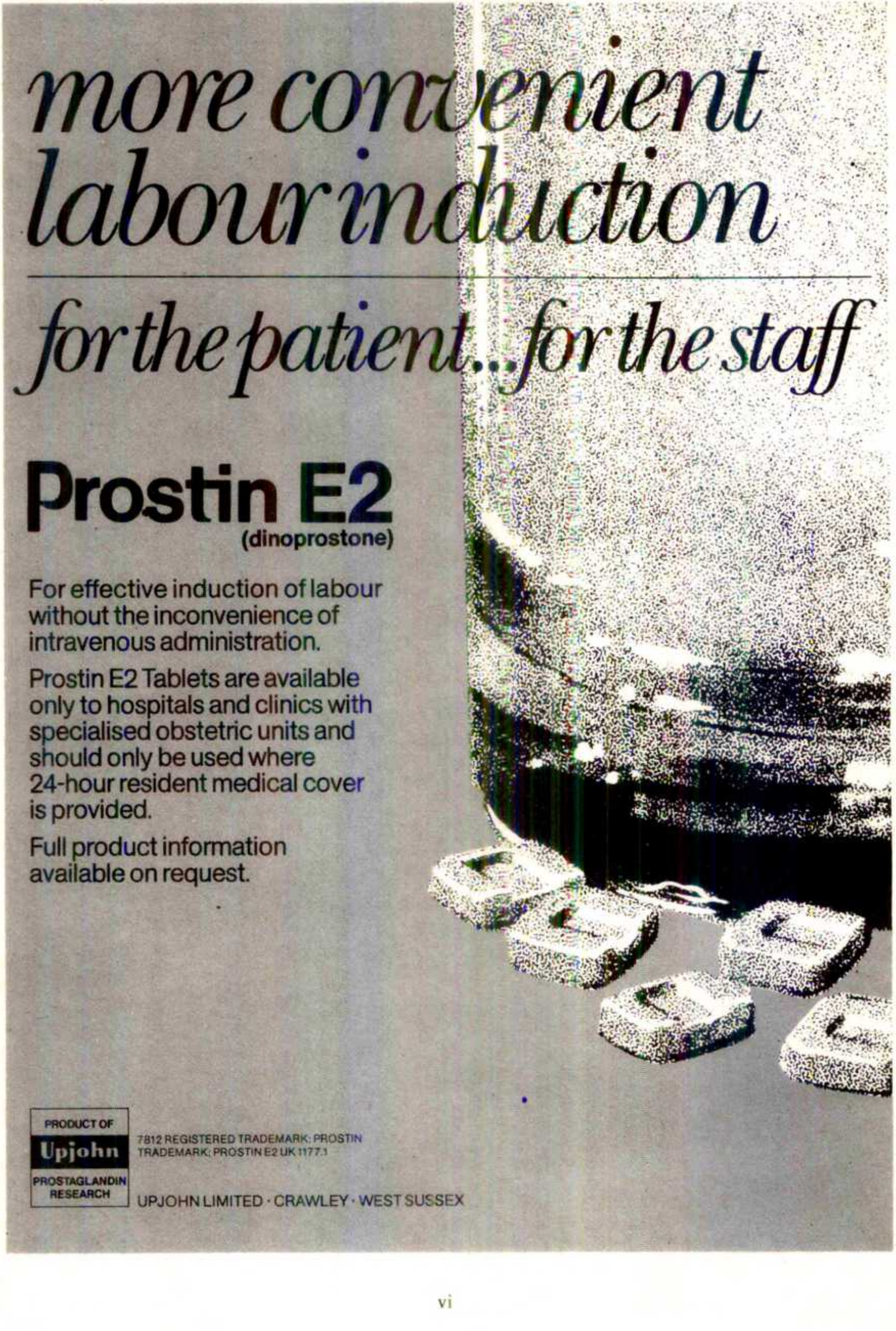

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1. J. int. med. Res. (1977) 5 (Suppl. 3): 86-91.
2. ibid., 101-108. **3.** ibid., 98-100.
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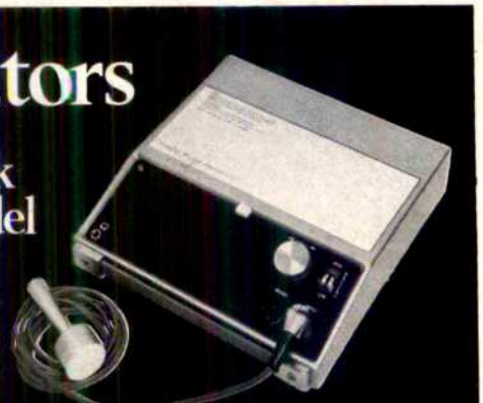

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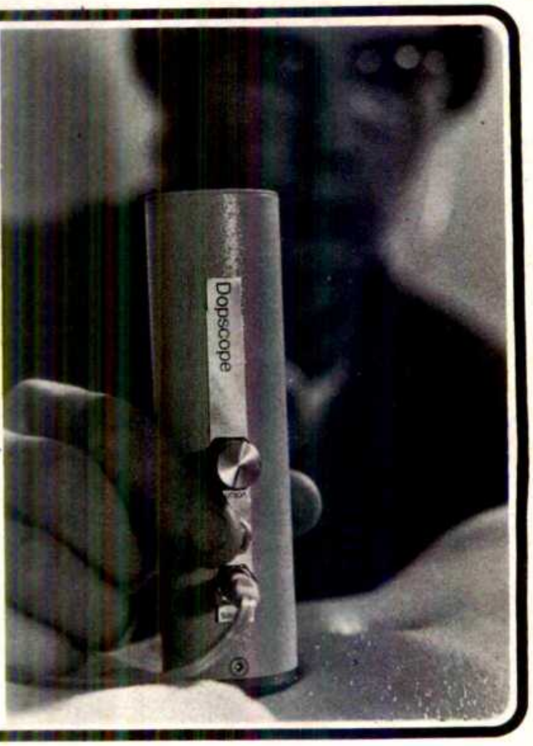

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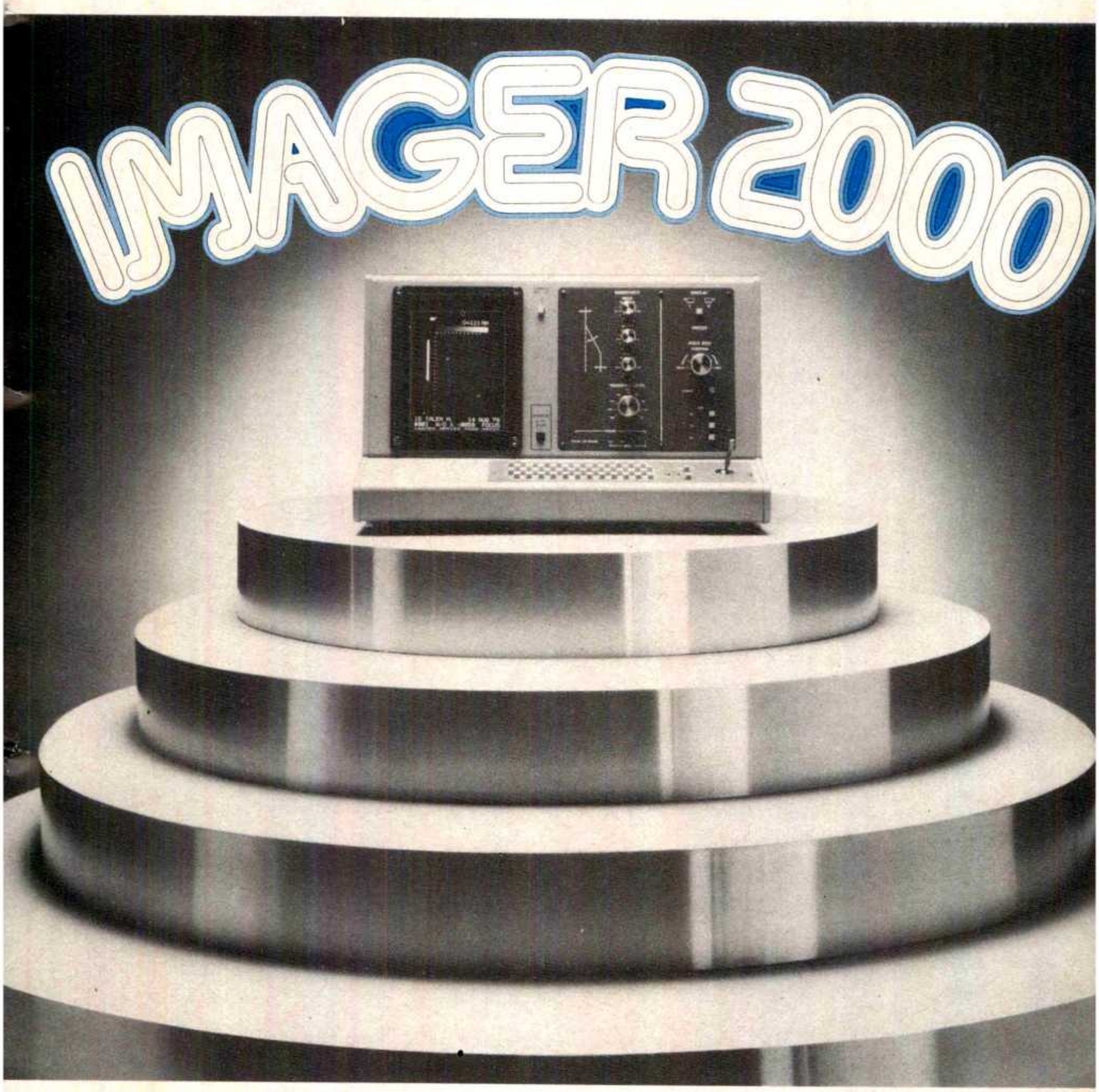

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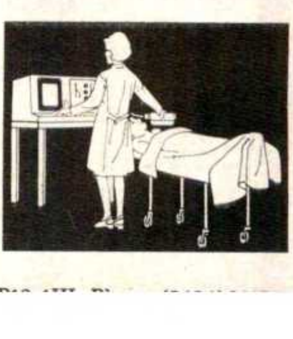

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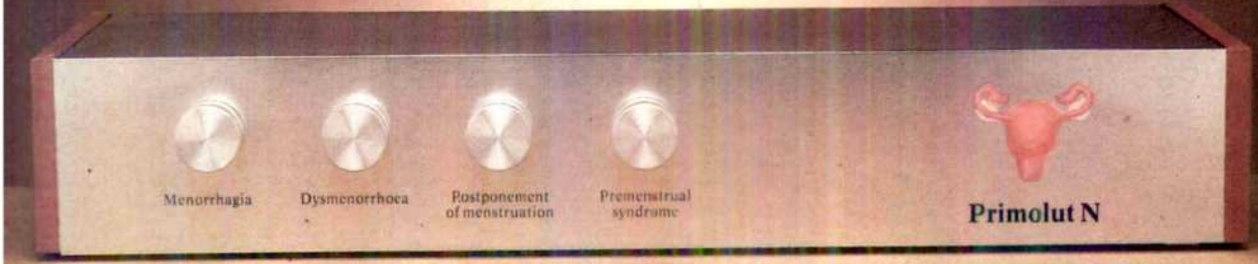

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THE OUTCOME OF PREGNANCY AFTER CONE BIOPSY OF THE CERVIX: A CASE-CONTROL STUDY

BY

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Summary

We investigated the outcome of pregnancy after cone biopsy of the cervix. We found that preterm delivery and low birth weight were commoner and the mean duration of labour longer in women who had a cone biopsy than amongst matched controls. Rapid labour (under two hours) was not significantly more common after cone biopsy.

MCLAREN *et al* (1974) described the outcome of 68 pregnancies among 50 women who had had a previous cone biopsy. They found a spontaneous abortion rate of 22 per cent and an incidence of premature labour of 7·5 per cent. McCann *et al* (1969) also studied 50 women with cone biopsies who had 74 subsequent pregnancies. They found a spontaneous abortion rate of 12 per cent and an incidence of premature labour of 9·5 per cent. Neither study had any comparative data.

We have studied the outcome of singleton pregnancies proceeding beyond 28 weeks gestation in women who have had a cone biopsy and compared them with matched controls.

METHODS

Patients

Detailed clinical records are available from the Cardiff Cervical Cytology Study (Landsman *et al*, 1977; Hibbard *et al*, 1979) for all women who have had a cone biopsy in Cardiff. Between February 1965 and April 1974, 600 women had a cone biopsy: 372 of these women were potentially fertile and up to April 1975, 76 had had 91 pregnancies after the cone biopsy (Table I). Thirteen pregnancies (14 per cent) aborted spontaneously, 11 (12 per cent) were terminated and there was one twin pregnancy. It was not possible to determine with any accuracy the cause of the spontaneous abortions but none was associated with gross pathology of the conceptus. Three of the abortions before 16 weeks gestation were attributed to the cone biopsy.

There were thus 66 singleton pregnancies which proceeded beyond 28 weeks gestation. Of these, 55 (including 4 primigravidae) were first pregnancies after the cone biopsy, 10 were second pregnancies and one was a third preg-

TABLE I

Outcome of 91 pregnancies after cone biopsy

Outcome	Order of pregnancy after cone biopsy First	Second	Third	Total
Therapeutic abortion	10	0	1	11
Spontaneous abortion				
< 16 weeks	8	1	0	9
16–28 weeks	3	1	0	4
Singleton births after 28 weeks	55	10	1	66
Twin birth	0	1	0	1
Total	76	13	2	91

nancy, and these form the basis for the case-control study. The case-control method was chosen because, as might be expected, the cone biopsy patients had a higher maternal age and parity and lower social class tnan the overall parturient population.

Controls

The Cardiff Birth Survey (Andrews, 1973) records details of all births to Cardiff residents. From this register four controls were selected to match each of our index patients in respect of five characteristics: (1) Singleton birth. (2) Maternal age (within 5 year age groups). (3) Parity (0, 1, 2, 3, 4, 5 or more). (4) Social Class (I and II, III, IV, V, Unclassified). (5) Date of delivery (same month or immediately preceding or following month).

With the above matching characteristics, 4 controls were obtained for 55 of the 66 index patients. To obtain 4 controls for each of the remaining 11 index patients, some of the matching characteristics had to be relaxed; social classes IV, V and unclassified were combined and delivery within the same calendar year was accepted.

Outcome of pregnancy

The outcome of pregnancy was assessed using five criteria: (1) Preterm delivery (less than 37 weeks). (2) Method of delivery. (3) Duration of labour. (4) Birth weight less than 2500 g. (5) Perinatal death.

Statistical analysis

The results were evaluated using the methods described by Pike and Morrow (1970) for case-control studies with more than one control per case.

RESULTS

The data for preterm delivery, method of delivery and birth weight are given in Table II.

Preterm delivery, method of delivery and birth weight (Table II)

There were 11 (17 per cent) spontaneous and one (1·5 per cent) induced preterm labours and deliveries among the 66 pregnancies after cone biopsy as compared with 8 (3 per cent) spontaneous and 6 (2 per cent) induced preterm labours and deliveries among the 264 controls. The differences in incidences for all preterm deliveries and for those occurring spontaneously are both statistically significant ($P < 0 \cdot 01$).

The increased risk of spontaneous preterm delivery was greater in the second than in the first pregnancy after cone biopsy. Six (11 per cent) of the 55 first pregnancies after cone biopsy and 4 (40 per cent) of the 10 second pregnancies ended in spontaneous preterm delivery. The single third pregnancy after cone biopsy resulted in a spontaneous preterm delivery.

Assisted delivery and Caesarean section were more common among the cone biopsy patients

TABLE II

Outcome of pregnancy after cone biopsy

Outcome	Cone biopsy group (n = 66)		Control group (n = 264)		Relative risk
	No.	Per cent	No.	Per cent	
Delivery before 37 weeks	12	18	14	5	3·4 p <0·01
Spontaneous only	11	17	8	3	5·5 p <0·01
All assisted deliveries*	15	23	37	14	1·6 NS
Caesarean section only	7	11	16	6	1·7 NS
Birth weight below 2500 g	14	21	22	8	2·5 p <0·01

* Caesarean section, forceps or ventouse.
NS = Not significant.

but the differences were not statistically significant.

The difference in birth weights shown in Table II was statistically significant (P <0·01). However, the weights of all infants in the cone biopsy group were assessed according to the tables of Thomson *et al* (1968) and the distribution was exactly as expected for their gestational ages.

Duration of labour (Table III)

Data on the duration of labour were based on the 55 multigravidae delivered vaginally for whom full details were available, and their 205 controls. The mean duration of labour was 8·5 hours for the cone biopsy group and 6·3 hours for the control group (P <0·01). Labour exceeded 12 hours in 11 index patients (20 per cent) and 21 controls (10·2 per cent). Rapid labour (under two hours) occurred in five cone biopsy patients (9·1 per cent) compared with 15 controls (7·3 per cent).

Labour was terminated by Caesarean section in three cone biopsy patients and two controls. In one cone biopsy patient labour had already exceeded 36 hours. In all other patients a Caesarean section was done before 12 hours of labour.

Perinatal mortality

There was one stillbirth, and one early neonatal death (due to congenital heart disease) among the 66 cone biopsy patients. One stillbirth and two early neonatal deaths occurred among the 264 controls.

DISCUSSION

McCann *et al* (1969) concluded that "sharp conization of the cervix does not significantly interfere with ability to carry the pregnancy to term or childbirth". This optimistic view was not borne out by our study, in which the outcome was worse in the cone biopsy group for most of the factors measured and reached levels of statistical significance for spontaneous preterm delivery, low birth weight (<2500 g) and mean duration of labour. The absolute magnitude of the differences in the various factors studied was generally large even though levels of statistical significance were not always reached. Contrary to commonly held belief, rapid labour was not significantly more common following cone biopsy.

The possible adverse effects of cone biopsy and their influence on the attitudes of the obstetrician is reinforced by inspection of the clinical notes. The history of cone biopsy sometimes influenced the decision as to the method of delivery. It was the principal stated factor in 2 of the 4 elective Caesarean sections and a contributory factor in the other two. One of the three emergency Caesarean sections was done after 12 hours of labour because of a pinhole cervical os attributed to cervical stenosis following cone biopsy; in one patient, a Caesarean hysterectomy was necessary because of rupture of the uterus at 30 weeks gestation. The only Caesarean section in which cone biopsy was not mentioned either as a direct indication or as a contributory factor was done

TABLE III

Duration of labour in multigravidae delivered vaginally

Group	No. of patients	Mean	Duration of labour (hours)									
			≧2		2·1–6		6·1–12		12·1–18		<18	
			No.	per cent	No.	per cent	No.	per cent	No.	per cent	No.	per cent
Cone biopsy	55	8·5	5	9·1	15	27·3	24	43·6	8	14·5	3	5·5
Control	205	6·3	15	7·3	108	52·7	61	29·8	15	7·3	6	2·9

because of prolapse of the umbilical cord in the first stage of labour.

Although previous cone biopsy was not the indication for terminating pregnancy in any of the women who had therapeutic abortion, the method of termination, by hysterectomy, was attributed to the previous cone biopsy in 2 of the 11 women. It was not possible to assess the risk of abortion due to previous cone biopsy. Although the overall rate (14 per cent) was not exceptionally high, in 3 of the 4 spontaneous abortions occurring after 16 weeks gestation the cone biopsy was thought by the obstetrician to have been the cause. One abortion at 20 weeks was in a patient who, when first examined at 19 weeks at the antenatal booking clinic, was found to have a shallow cervix with a gaping cervical os, through which the membranes were protruding. Her previous obstetric history had been uncomplicated. Two abortions at 20 weeks occurred in one patient in spite of a cervical suture during early pregnancy on each occasion. Before cone biopsy she had had an uncomplicated obstetric history.

One of the underlying assumptions of the test of significance is that the outcome of each pregnancy in an individual woman is independent of the outcome of all others, which is not true if first and second pregnancies following cone biopsy are considered together. This may have had the effect of overestimating the level of statistical significance but it was likely to have been small. It must also be remembered that the various outcome measures themselves are interdependent to varying degree. This is well illustrated by the finding that the relatively high incidence of low birth weight is attributed to preterm delivery rather than intrauterine growth retardation. Also, the high proportion of small babies delivered before term in the cone biopsy group may have the effect of reducing the mean duration of labour.

It is clear that patients who have had cone biopsies are liable to more pathological events in subsequent pregnancies. Patients should be instructed to seek medical advice early and should be supervised closely throughout pregnancy.

ACKNOWLEDGEMENTS

This paper is derived from material from the Cardiff Cervical Cytology Study and the Cardiff Birth Survey. We thank all who are involved in these projects and those who have contributed in any way towards them.

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A STUDY OF CRYOSURGERY FOR DYSPLASIA AND CARCINOMA *IN SITU* OF THE UTERINE CERVIX

BY

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Summary

We studied 22 patients with a histopathological diagnosis of severe dysplasia and 89 patients with a diagnosis of carcinoma *in situ* of the uterine cervix. Twenty patients (18 per cent) had negative cervical smears for four to six years after diagnosis by biopsy of the cervix. The 91 patients with persistently abnormal smears were treated by cryosurgery, using a double freeze technique with nitrous oxide. Seventy-four (86 per cent) had persistently normal cervical smears after one treatment and eight after a second treatment while nine patients required conization for recurrently abnormal cervical smears. The duration of follow-up was five or six years in 48 patients (53 per cent). In a subsidiary study, material was obtained for histological examination from 72 patients with normal smears by endocervical curettage and multiple biopsies of the cervix; 8 showed slight atypia and 2 had residual carcinoma *in situ*.

RECENTLY there has been increasing interest in cryosurgery for benign and premalignant lesions of the uterine cervix (Ostergard *et al*, 1968; Townsend *et al*, 1971; Ghoneim *et al*, 1971; Popkin *et al*, 1978; Einerth, 1978; Kaufman and Irwin, 1978). However, the results have often been difficult to judge because treatment followed conization or multiple biopsies, which may have removed the primary lesion.

We tried to evaluate the effect of cryosurgery on patients with abnormal cervical smears after a diagnosis of dysplasia or carcinoma *in situ* of the uterine cervix had been made by histological examination of a punch biopsy specimen.

PATIENTS

Only women less than 40 years of age were included in the study. They were selected during a two-year period (December 72 to December 74) from patients referred from the outpatient department to the colposcopy clinic because of an abnormal cervical smear suggesting a diagnosis of dysplasia or carcinoma *in situ*. After a history had been taken, patients had a repeat cervical smear and a colposcopically directed biopsy. The biopsies were taken from areas with white epithelium or an abnormal vascular pattern as indicated by a mosaicism or punctation. If no colposcopic abnormalities were noted, several biopsies were taken from the transformation zone. Five biopsies were obtained from most patients and an endocervical curettage was done if the squamocolumnar junction was not adequately seen.

Only patients with a histological diagnosis of dysplasia or carcinoma *in situ* were referred for possible cryosurgery. The two-year period produced 111 suitable patients, 22 with a histo-

TABLE I
Age of patients at diagnosis

Age (years)	Number of patients		
	Severe dysplasia	Carcinoma *in situ*	Total
–19	2	1	3
20–24	4	17	21
25–29	5	37	42
30–34	6	21	27
35–39	5	13	18
Total	22	89	111

Average age: 28·6 years

pathological diagnosis of dysplasia and 89 with a carcinoma *in situ*. At the time of diagnosis the patients' ages ranged from 18 to 39 and 66 patients (59·5 per cent) were less than 30 years of age (Table I). Thirteen patients were nulliparous and 36 had only one child; the mean parity was 1·8.

METHODS

The cryosurgical treatment was given with TCC 10 Spembly Cryosurgical Unit (Andover, UK). Liquid nitrous oxide was used as refrigerant. Irrespective of the size of the lesion, we used a 25 mm diameter cone-shaped cervical probe with a 20 mm endocervical extension. All patients had cryosurgery during the week after the end of a menstrual period as outpatients and without anaesthesia. An intrauterine device, when present, was left in place during cryosurgery. A self-retaining bivalve speculum was inserted into the vagina. The probe was lightly pressed against the cervix, which was kept fixed with a single-hooked volsellum applied to each lateral fornix. We used a double freezing technique with a three-minute freeze, a three-minute thaw, and then a further three-minute freeze. Patients were warned that they might have a watery discharge for two to four weeks and that it might be blood-stained during the first two weeks. Patients were advised against intercourse while they had heavy discharge. Cervical smears were taken three months after the diagnostic biopsy, three months after cryosurgery, then after an interval of six months and finally at yearly intervals providing there was no cytological abnormality. Material for further histological examination was also obtained by multiple biopsy and endocervical curettage in 72 patients with negative smears.

RESULTS

Of the 111 patients who were candidates for cryosurgery because of a histological diagnosis of severe dysplasia or carcinoma *in situ*, 20 (18 per cent) had persistently normal smears; 12 of them (7 with carcinoma *in situ*) were observed for four to five years, and 8 (7 with carcinoma *in situ*) for five to six years. Of the remaining 91 patients, 77 (85 per cent) had abnormal cells in cervical smears taken within one year of the diagnostic biopsy while the remainder developed abnormal smears at a later time (see Table II).

Of the 91 patients treated by cryosurgery, the biopsy had shown severe dysplasia in 16 and carcinoma *in situ* in 75. After one treatment by cryosurgery, 74 patients (86 per cent) developed normal smears for the duration of the period of observation (Table III).

Of the 17 patients who had abnormal smears after initial cryosurgery, 11 had further cryosurgery (and 8 developed normal smears) while

TABLE II
Abnormal smears after biopsy showing severe dysplasia or carcinoma in situ

Time after biopsy (months)	Slight–moderately	Severely abnormal cells	Cells suggestive of carcinoma *in situ*	Total
Less than 12	28	16	33	77
12–23	2	1	0	3
24–35	1	1	5	7
36–47	0	0	2	2
48–59			2	2
Total	31	18	42	91

TABLE III

Results of first cryosurgical treatment

Pretreatment cytology suggestive of:	No. of patients	Negative cytology	
		No.	Per cent
Slight–moderate dysplasia	32	29	97
Severe dysplasia	17	13	89
Carcinoma *in situ*	42	32	76
Total	91	74	86

TABLE IV

Interval between cryosurgical treatment and first subsequent abnormal smear

	3 months	6 months	One year	2 years	Total
After first cryosurgical treatment	12	1	2	2	17
After second cryosurgical treatment	7	1	2	1	11
Total	19	2	4	3	

6 patients had a conization. This gives a total cure rate of 90 per cent during the period of observation. The intervals between cryosurgical treatment and the first subsequent abnormal smear are shown in Table IV.

Three patients had conization because of an abnormal smear after the second session of cryosurgery making a total of nine patients who had conization. Eight of the patients had normal cervical smears after conization. One patient, who had two smears indicating severe dysplasia, had a repeat conization which showed severe dysplasia and since then has had normal cervical smears.

The duration of follow-up for the 91 patients who had cryosurgery and/or conization leading to normal cervical smears is shown in Table V.

TABLE V

Duration of follow-up after cryosurgery and/or conization resulting in normal subsequent smears

Treatment	Duration of follow-up (years)			Total
	0–2	3–4	5–6	
First cryosurgery	5	24	45	74
Second cryosurgery	2	5	1	8
Conization		6	2	8
Reconization	1			1
Total	8	35	48	91

TABLE VI

Outcome of pregnancies after cryosurgery

	No.
Term deliveries (one Caesarean section for disproportion)	24
Premature infants (< 2·500 g)	2
Spontaneous abortion	1
Therapeutic abortions	5
Ectopic pregnancy	1
Total	33

Pregnancy after cryosurgery

There were 33 pregnancies after cryosurgery and the outcome of the pregnancies is shown in Table VI. One of the two low birth weight infants had a meningomyelocele. Two patients became pregnant respectively six weeks and four months after cryosurgery in spite of preceding secondary infertility of 18 months and 4 years' duration.

Special histological follow-up study

As cervical smears can be falsely negative in up to 20 per cent of cases (Selim *et al*, 1973) biopsies were taken from the ectocervix and the endocervix was curetted one year after cryosurgery in 56 patients after the first treatment and in 6 patients after their second treatment by cryosurgery. Fifty-three of the patients had negative biopsies, seven showed slight atypia, and two had residual carcinoma *in situ*. Without any further measures, all subsequent cervical smears were negative. Of the 20 patients who had normal smears after the initial diagnostic

LLEGE OF MEDICINE BRARY

biopsy, 10 were similarly examined. Nine had no residual disease, and one had slight atypia requiring no further treatment.

DISCUSSION

The results from this study strongly support earlier reports on cryosurgery as an effective therapy of preinvasive cervical carcinoma and allied conditions (Townsend and Ostergard, 1971; Einerth, 1978). As a criterion of effective treatment, two consecutive negative cytological tests taken at a three-month interval have often been suggested (Tredway *et al*, 1972; Einerth, 1978). With us, however, only patients with remaining negative vaginal smears during the entire follow-up period were considered cured. In this study, diagnostic biopsy alone was curative in 18 per cent of patients. To assess the curative effect of a new treatment, it is mandatory to treat only patients with residual lesions after diagnostic biopsy.

It was mentioned in the introduction that an endocervical curettage was performed if the squamocolumnar junction was not adequately seen. This is not according to a now generally accepted view that conservative treatment should only be made when the whole transformation zone is visible with the colposcope. However, this study was started when this opinion was less axiomatic. Anyhow, no case of invasive carcinoma was later proven to have been missed in this study.

Earlier investigations of cryosurgical treatment of severe dysplasia or carcinoma *in situ* with remaining cervical dysplasia after diagnostic biopsy showed a cure rate of 89 per cent (Townsend and Ostergard, 1971) and 91 per cent (Einerth, 1978).

But the observation period, in these investigations was short (from seven months to three years) and the criteria of success were more limited than ours, which showed a cure rate of 90 per cent. More than half of our patients were observed for more than five years, and 40 per cent for three to four years. Our cure rate would probably have been 95 per cent if the six patients who had conization after the first treatment by cryosurgery had had further cryosurgery.

Follow-up endocervical curettage and multiple biopsies of the cervix taken at one year after the cryosurgery revealed mild clinically insignificant atypia in 7 of the 56 patients appropriately studied.

Small areas of residual carcinoma *in situ* were detected in biopsies from two patients with negative cervical smears after cryosurgery. Both patients subsequently still had negative smears and repeat biopsies and endocervical curettage showed no histological abnormality. It has been suggested that carcinoma *in situ* involving the gland crypts could be covered by squamous epithelium after cryosurgery and thus not give rise to abnormal cytology (Chamberlain, 1975). We found no such inclusions but it must be admitted that the depth of our multiple biopsies rarely exceeded 4 mm and gland crypts are at 4 to 5 mm.

Expertise in colposcopy is a prerequisite for cryosurgical treatment of cervical intraepithelial neoplasia as is certainty about the patient's attendance for follow-up. Because the squamocolumnar junction moves inside the external cervical os with advancing age, cryosurgery should probably only be used in women under 40 years of age and it has advantages in those who desire further pregnancies. In the few patients in whom cryosurgery fails, conization might be indicated. While it is still not proven that cryosurgery is definitive long-term therapy for precancerous lesions of the cervix, information about the prolonged follow-up of patients treated by cryosurgery is necessary and we hope to report the results of such a study in due course.

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AN IMPROVED METHOD OF FETAL WEIGHT ESTIMATION USING ULTRASOUND MEASUREMENTS OF FETAL ABDOMINAL CIRCUMFERENCE

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Summary

A simple and accurate method is described for estimating fetal weight from a single fetal abdomen circumference measurement at the level of the umbilical vein. The abdominal circumference was converted into a weight centile for the maturity at the time of measurement so that the weight at delivery could be predicted. This method was tested on a population of fetuses presenting by the breech near term. Although the error between actual and predicted weights was 194 g (1 SD) for all the patients, for a large well-defined subgroup the error was much smaller, being only 104 g (1 SD).

BIRTH weight affects perinatal morbidity and mortality (Goldstein and Peckham, 1975). Preterm, and small-for-dates fetuses are especially at risk (Usher and McLean, 1974), and there could be a significant reduction in the perinatal death rate if fetal growth retardation could be diagnosed by 34 weeks gestation. Furthermore, in breech presentation, a knowledge of both fetal weight and maturity could significantly affect management of the delivery (Zatuchni and Andros, 1965). Maturity and weight estimations are therefore of considerable significance as is evident from the large number of ultrasound methods which have been developed to assess them.

The crown–rump length (CRL) measurement (Robinson, 1973) and the biparietal diameter (BPD) measurement (Campbell and Newman, 1971) are both well established as indicators of fetal maturity. These techniques have been shown to be highly reliable in experienced hands (Robinson and Fleming, 1975; Poll, 1976).

Workers have used different methods to assess fetal weight and some of their results and ours are summarised in Table I while Figure 1 compares our results for fetal abdominal circumference measurement at various stages of gestation with those obtained by others.

Most of the methods listed in Table I give errors (expressed as one standard deviation) between predicted and actual weights of the order of ±250 g. To put these errors into perspective, Lind (1970) pointed out that guesswork alone, based on the normal distribution of birth weight, would give an error of about 440 g (1 SD).

The third sub-group of our data (see Table I) gave the most accurate weight prediction and only two other teams (Morrison and McLennan, 1976; Higginbottom *et al*, 1975) have achieved comparable results. However, the technique of Morrison and McLennan (1976) was very time-consuming because it involved calculations based on multiple closely spaced

TABLE I

The error between predicted and actual birth weights for previously published methods, compared with the results of the present study

Author	Method	1 SD (g)
Suzuki *et al*, 1974	Fetal heart volume	526
Cambell, 1974	BPD	405
Thompson and Makowski, 1971	BPD	350
Ylostalo and Jarvinen, 1974	BPD, body length, mid-body dimensions	317
Thompson, 1965	BPD + thorax circumference	307
Thompson and Makowski, 1971	BPD + chest diameter	290
Campogrande *et al*, 1977	BPD + body area + body circumference	287
Campbell and Wilkin, 1975	Abdominal circumference	279
Picker and Saunders, 1976	Trunk and limb volumes	241
Lunt and Chard, 1976	Skull area + thorax area	215
Hansmann *et al*, 1973	BPD + transverse thoracic diameter	178
Morrison and McLellan, 1976	Fetal volume from multiple scans	107
Higginbottom *et al*, 1975	Abdominal circumference	72
Poll, this study (1)	Abdominal circumference on all breech presentations using EDD alone to give fetal maturity	194
	Abdominal circumference on breech presentations using either:	
„ „ „ (2)	BPD before 30/52 to give fetal maturity	151
„ „ „ (3)	EDD when BPD and EDD consistent at 37/52+	104

BPD = biparietal diameter.
EDD = expected date of delivery.

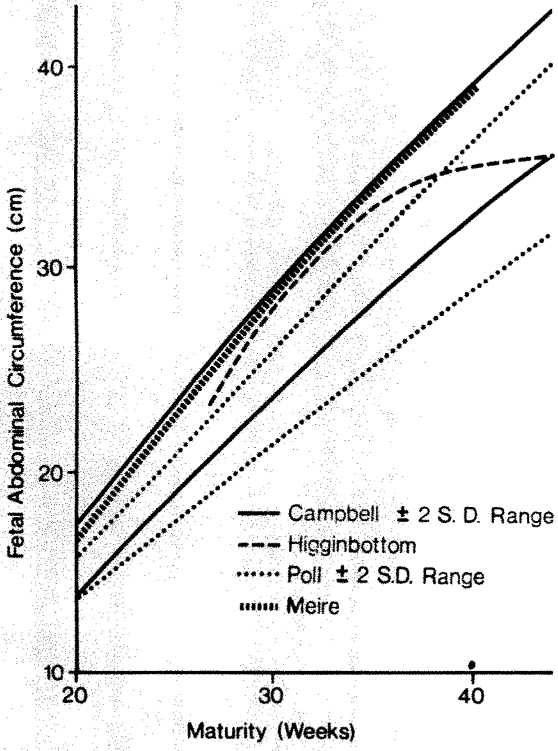

FIG. 1

The variation of fetal abdominal circumference with fetal maturity. Data derived from Campbell and Wilkin (1975); Higginbottom *et al* (1975); Meire (1977, personal communication); and Poll (this study).

scans. To compare our results with those of Higginbottom *et al* (1975) we converted their 'fetal weight' estimates to 'maturity' by using data from Thomson *et al* (1968) and the British Perinatal Survey (Butler and Alberman, 1969) for the weight of normal fetuses before 32 weeks. Figure 1 shows that the FAC growth curve we derived from their data was of markedly different shape to that of other workers.

Most authors have concentrated on predicting birth weight from measurements taken as close to the date of delivery as possible. The ideal method would provide an estimate of birth weight at any time during the second half of pregnancy and could be used to detect fetal growth retardation by finding changes in weight centiles as pregnancy progressed. The method we now describe is simple, accurate, and can predict birth weight from 20 weeks gestation onwards.

METHOD

A Nuclear Enterprises NE4102 ultrasound machine was used with a system velocity of 1540 m/second and with the electronic calipers adjusted for a velocity of sound of 1600 m/second.

BPD measurements were made using routine methods (Campbell, 1968; Poll, 1976). We use our own BPD-maturity graph constructed from longitudinal data, obtained at four weekly intervals, from normal patients. The difference between our curve and that provided by Campbell and Newman (1971) is small; a maximum of one week's difference at 14 and 40 weeks with the curves crossing at 38 weeks.

All fetal abdomen circumference (FAC) measurements were made at the level of the umbilical vein using a slight modification of the method of Campbell and Wilkin (1975). It was felt that a significant error could be introduced in the FAC if only a slight error was made in determining the position of the fetal spine, especially if this was markedly flexed. Consequently a series of scans were made at approximately right-angles to the fetal spine, and the position of the spine and approximate position of the umbilical vein marked on the maternal abdomen. These marks were then used to determine the exact lie of the spine to obtain the angles of tilt and rotation as described by Campbell and Wilkins (1975). Scans were routinely made at a magnification of 3/5 and photographed from the storage display by polaroid camera. The FAC was measured from the photograph using a map-measurer and this measurement was then multiplied by appropriate experimentally-determined correction factors to give a true full-size measurement.

As a preliminary to the weight study we constructed a graph of the variation of the normal values of the FAC with fetal maturity and this graph is included in Figure 1.

The method of estimating the delivery weight was as follows:

(a) Both the fetal BPD and abdominal circumference were measured and the expected date of delivery (EDD) was noted.

(b) The gestational age at the time of measurement was calculated to a precision of half a week from the current BPD, the EDD, or an earlier BPD or CRL. Figure 1 shows the estimated 2·3rd and 97·7th centiles (±2 SD) of FAC values from 20 weeks gestation onwards.

(c) The centile of the FAC measurement was calculated by noting the range in FAC between that actually measured and that corresponding to the −2 SD centile, and dividing this range by the range in values between the −2 SD and the +2 SD centiles. The resultant ratio was converted to an equivalent centile using a table or graph (Fig. 2) of the Gaussian curve.

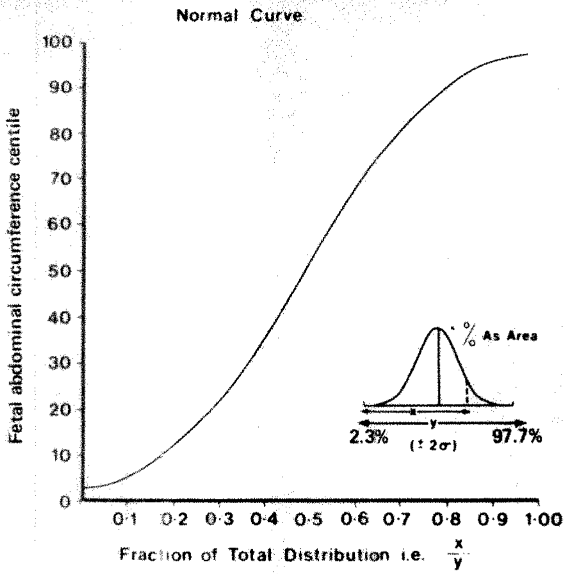

FIG. 2

The curve used to convert fetal abdominal circumference measurement to a weight centile, given the values of abdominal circumference corresponding to the 2·3rd and 97·7th centiles.

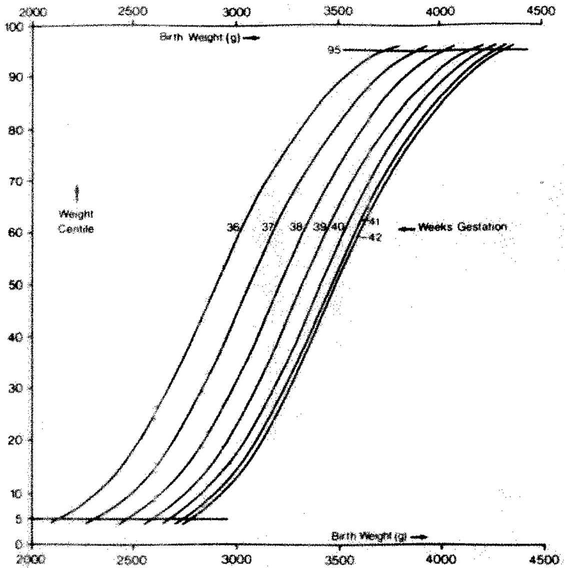

FIG. 3

Birth weight distributions for fetal maturities near term (Thomson *et al*, 1968).

(d) To a first approximation the FAC centile so derived can be equated to the weight centile. The predicted weight at term (or earlier) can then be read from the data on birth weight at delivery given by Thomson *et al* (1968) (Fig. 3).

(e) When the quantity minus 'actual estimated birth weight' was plotted against the fetal abdominal circumference centile for all patients, the distribution obtained was skewed, with an overprediction of weight at high FAC centiles. A regression analysis upon these data furnished a correction factor of the form 'A+Bx(FAC centile) + Cx(FAC Centile)^2, to the weight prediction as determined in (d). The actual correction factors depended upon the criteria of fetal maturity used in (b), and were necessary because the method contained several assumptions and potential sources of error. These included the assumed equivalence of the FAC and weight centiles, the assumed Gaussian distribution of FAC values for any given maturity (the data is consistent with a Gaussian distribution), the difficulty of accurately determining the true ±2 SD ranges in FAC and also errors which will always tend to overestimate birth weight such as errors in obtaining the FAC and possible growth retardation between the times of scanning and delivery.

RESULTS

Our results are from patients selected at a routine antenatal examination solely on the basis of the fetus presenting by the breech at a gestation of 37 weeks or more. For most patients there was an interval of up to three weeks between scanning and delivery. The weight prediction exercise was part of a survey to assess the significance of the BPD and weight measurements in the management of a pregnancy complicated by fetal breech presentation.

It was noticed at the ultrasound examination that many of the patients had a fetal BPD which was smaller than one would expect from menstrual data (often by the equivalent of three weeks or more). Weight predictions were made using both the BPD and EDD maturities. Figure 4 shows the errors between the actual and predicted birth weight for both these maturities for the first few patients. The errors obtained using the EDD were approximately symmetrically distributed about the zero-error line but a large percentage of results using the BPD gave unacceptably high errors of more than 400 g. It was therefore concluded that the BPD near term was an unreliable indicator of fetal maturity especially when assessing fetal weight.

If the EDD maturities were used, then the error between predicted and actual birth weights was 194 g (1 SD)—of the same order as found by other workers (Table II). If, however, the maturity was based on a BPD measurement obtained before 30 weeks (as calculated by the EDD) then the error between predicted and actual birth weights was 151 g (1 SD) with 16 out of 22 patients within ±175 g.

Our best results were consistently obtained in those patients in whom, at the time of FAC measurement, the BPD maturity was within one week of that calculated from menstrual data. For these patients the error was only 104 g (1 SD) with 22 out of 25 patients within ±175 g. This figure is considerably better than those obtained by most other workers.

DISCUSSION

Our method possesses many of the characteristics needed if birth weight estimation by ultrasound is to be used routinely in antenatal care. The technique is simple, accurate and can give a longitudinal picture of fetal growth.

A full analysis of statistical variation in our results using the above methodology is complex. There are not only simple measurement errors in the BPD and FAC themselves, but there are also normal ranges of BPD and FAC for any given maturity (Campbell and Newman, 1971) and weight (Campbell and Wilkin, 1975). The final complication is that a given error in maturity or FAC centile will produce different weight errors depending upon the combination of the absolute values of these factors.

The accuracy of the technique seems to depend on the BPD at the time of the measurement of the FAC and on the availability of a maturity calculated from an early BPD. The choice of 30 weeks for one of the subgroups was based upon

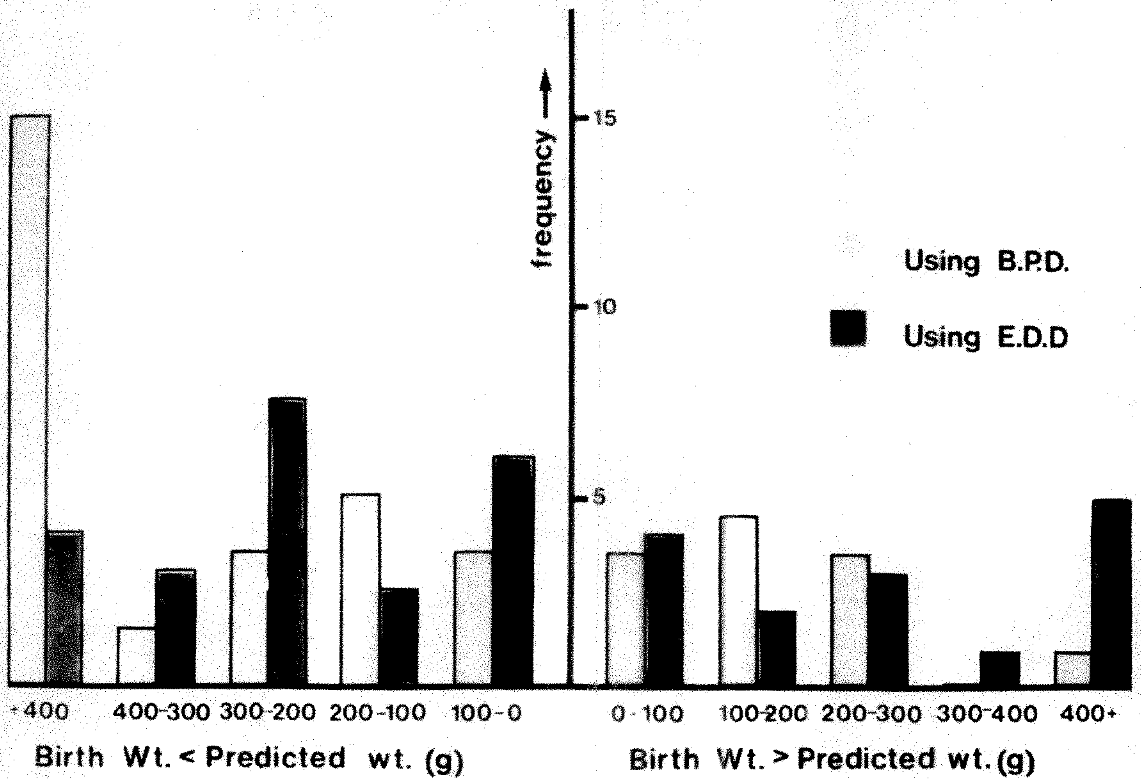

FIG. 4
Errors between actual and predicted fetal weights for the first few patients seen.

TABLE II
The accuracy of weight predictions in the present study

Maturity calculated using	Number of patients	Accuracy	
		2 SD (g)	Distribution of results
EDD alone	65	±388	55/65 within ±300 g
EDD when BPD ≃ EDD at 37 weeks plus	25	±208	22/25 within ±175 g
CRL or BPD (measured before 30 weeks)	22	±302	16/22 within ±175 g

CRL = crown–rump length.
EDD = expected date of delivery.
BPD = biparietal diameter.

our clinical experience that up to this maturity BPD growth is usually normal (regardless of subsequent fetal growth patterns) and the normal range in BPD readings is relatively small.

Small BPD measurement errors (equivalent to less than one week) are, in general, of little consequence. Thus an underestimate of fetal maturity will result in the fetus delivering at an apparently lesser maturity but at an increased FAC centile (and *vice versa*). However, this is only a partial explanation of the accuracy of the weight estimations within the two data subgroups. A fuller explanation necessitates the reasonable hypothesis that there is some correlation between BPD and FAC, so that if the BPD, for example, is larger than average for a given maturity (and hence the fetus is assigned an incorrect maturity), then the FAC will also be above average.

Our greatest errors occurred when we estimated the abdominal circumference (and therefore the weight) as above the 80th centile.

Although this overestimate could lead to unnecessary Caesarean section with fetal breech presentation, all these babies were heavier than 3·4 kg when delivered near term and were thus potentially unsuitable for vaginal delivery. The practical effect of such errors is thus small.

Our smallest errors occurred with the small and average weight fetuses, and these, especially if within the two subgroups, can be identified with considerable precision (43 out of 47 within ±200 g). It is thus possible to identify accurately the small-for-dates fetus.

The two subgroups were chosen to test the hypothesis that most of the large errors in our original data were due to errors in estimation of fetal maturity. Our statistics show this can be only a partial explanation, and there are probably other factors, possibly associated with the absolute size and shape of the fetal skull.

It should be added that none of the groups differ significantly ($P<0 \cdot 05$) from each other in terms of birth weights.

There are several other points of importance relating to the FAC and BPD which arise from this study. Firstly, there is a considerable difference between our fetal abdominal circumference/maturity graph (Fig. 1), that used by Campbell [1975, personal communication; but approximately the same information can be obtained by combining the data given by Campbell and Wilkin (1975) with that of Thomson *et al* (1968)] and provisional data provided by H. Meire (1977, personal communication) after correcting for each systems magnification and linearity. Although the discrepancies are not readily explicable, all sets of information appear reliable in the hands of their respective authors. Thus ultrasound departments must not rely upon published data but should construct their own BPD and FAC curves.

A BPD measurement before 30 weeks would now seem an absolute necessity for accurate diagnosis of maturity (Campbell, 1968) and hence a relatively accurate prediction of birth weight.

The interpretation of a BPD measurement near term in the fetus presenting by the breech should be regarded with some suspicion as these measurements are frequently below the accepted norms (even with a normally growing fetus). This may be due to differences between fetal skull shapes with breech and vertex presentations.

Probably the greatest advantage of our method of fetal weight estimation is that it allows a longitudinal study of fetal weight throughout the third trimester. It is therefore possible that our method would detect fetal growth retardation better than would serial BPD measurements (Campbell, 1974) or head circumference/abdominal circumference ratios (Campbell and Thoms, 1977) since confusion caused by symmetrical or asymmetrical growth retardation patterns would not exist.

Our data are retrospective but a prospective study is in progress.

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CHANGES IN FAT, FAT-FREE MASS AND BODY WATER IN HUMAN NORMAL PREGNANCY

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Summary

Measurements of body weight, total body water and total body potassium (^{40}K) were made serially on three occasions during pregnancy and once post partum in 27 normal pregnant women. Skinfold thickness and fat cell diameter were also measured. A model of body composition was formulated to permit the estimation of changes in fat, lean tissue and water content of the maternal body. Total maternal body fat increased during pregnancy, reaching a peak towards the end of the second trimester before diminishing. Serial measurements of fat cell diameter showed poor correlation, whilst total body fat calculated from skinfold thickness correlated well with our estimated values for total body fat in pregnancy.

ALTHOUGH measurements on rats have demonstrated that a considerable increase in body fat occurs during pregnancy (Spray, 1950; Flanagan, 1964), studies done during human pregnancy have produced variable results. Hytten and Leitch (1971), largely from the results of body water measurements, suggested that pregnant women store body fat at least up to 30 weeks gestation to provide an energy bank. On the other hand, a study on a randomized series of pregnant, non-pregnant and postpartum women (Seitchik, 1967) did not show a consistent trend for fat deposition. A recent investigation (Emerson *et al*, 1975), in which serial measurements were made on a small group of patients maintained on controlled diet, concluded that in normal pregnant women the storage of body fat is regulated by the energy content of the diet, as in non-pregnant women.

The present work was undertaken to examine further the question of fat storage by means of a longitudinal study designed to establish changes in adipose tissue mass and fat cell size in normal pregnancy. This necessitated the formulation of a model of body composition from measurements of body weight, total body water and total body potassium. The model also allowed changes of lean tissue and of interstitial water of the maternal body to be examined.

PATIENTS AND METHODS

Twenty seven normal pregnant women aged 19 to 40 years were studied. Their body weights in early pregnancy ranged from 48 to 66 kg and did not differ by more than 20 per cent from their expected weights, based on height and age (Society of Actuaries Tables, 1959). Nineteen patients were primigravidae. The pregnancies were uncomplicated and no patient was delivered before the 38th completed week. No dietary restriction was employed.

During pregnancy, serial measurements were made on three occasions on each patient; at 10 to 14 weeks, 24 to 28 weeks and at 36 to 38 weeks gestational age, calculated from the date of the last menstrual period. On all but one patient, a fourth measurement was made between 6 and 15 weeks after delivery. Body weight, total body water, total body potassium, skinfold thickness and fat cell diameter were measured on each occasion. Patients were weighed wearing only a light hospital gown of known weight. The consent of patients was obtained for the study which was approved by the Hospital Ethics Committee.

Skinfold thickness

Skinfold thicknesses were measured on the left side of the body in triplicate at four sites; over the mid point of the biceps and triceps muscles, below the inferior angle of the scapula, and above the supra-iliac crest (Durnin and Rahaman, 1967) using Meikosha calipers with faces of 20 mm^2 and which exerted a constant pressure of 10 g/mm^2. The results at each site were averaged, and the values at the four sites added.

Total body water

Total body water (TBW) was estimated by isotope dilution using deuterium oxide (D_2O). Two to four g of 99·8 per cent D_2O in 60 g tap water were administered orally, immediately after the patient had emptied her bladder and a baseline urine sample had been obtained. Doses were standardized by weighing. After a period of 4 to 5 hours to allow the dose to equilibrate within the body water pool, a blood sample was obtained. During the equilibration period the patient was allowed only one small drink (about 150 ml) not less than 90 minutes before the blood sample was taken. All urine passed during the equilibration period was collected and weighed and an aliquot retained for isotopic analysis. Urine and plasma samples were stored at −20°C and subsequently analysed by mass spectrometry to determine their deuterium contents (Halliday and Miller, 1977).

Total body potassium (TBK)

Measurements of TBK were made using a liquid scintillator whole-body counter (Smith and Cronquist, 1977). Measurements on patients were made for 1000 seconds, and standard errors, including counting statistics and calibration errors, ranged from 3·6 to 5·2 per cent of the observed values. The counter had previously been calibrated using ^{42}K in a group of subjects which included normal and obese females (Smith *et al*, 1979) and calibration factors (counts/second per g of potassium) were related to (weight/height)$^{\frac{1}{2}}$. In the present study, changes in counting efficiency due to alterations in body shape of each patient during pregnancy were allowed for by using the above relationship to obtain the appropriate calibration factor at each measurement.

Fat cell diameter

Samples of adipose tissue were aspirated from the subcutaneous area over the upper outer quadrant of the right buttock (Hirsch *et al*, 1960). The skin was anaesthetised with one per cent lignocaine before the insertion of a thin-walled (no. 16) needle. About one ml of sterile isotonic saline was injected through the needle from a 20 ml syringe. With an assistant grasping the layer of skin and adipose tissue, maximum traction was applied to the syringe plunger, and the needle was pushed back and forth in the adipose tissue. Numerous small shreds of adipose tissue were thus obtained. These were placed in polythene tubes with 0·2 ml of buffer containing one per cent plasma bovine albumin and 0·5 per cent collagenase and incubated in a shaking water bath for ten minutes at 37°C (Di Girolamo *et al*, 1971). Four drops of the suspension of adipose cells were placed in the well of a graduated glass slide and stained with one drop of one per cent methylene blue. The cells were examined at a magnification of × 120, with a Zeiss microscope equipped with a Polaroid camera attachment. The free fat cells were recognized by their spherical shape and stained cytoplasm and could readily be distinguished from lipid droplets. Four or five different fields were photographed so that between 100 and 150 cells from the same sample of adipose tissue could be measured with the aid of a scale photographed from the graduated glass slide. The mean of the fat cell diameter was calculated.

Calculation of expected values

Expected values of body weight, TBK and TBW were calculated for the early pregnancy (10 to 14 weeks) and postpartum measurement periods. Expected values of body weight were estimated from the Society of Actuaries Tables (1959) using the subject's height and age; expected values of TBK were calculated from a regression equation based on height, weight and age (Boddy *et al*, 1972) which has been shown to be valid for the whole-body counter used in the present study (Smith *et al*, 1979); and expected values of TBW were derived from a regression equation based on weight and height (Skrabal *et al*, 1973).

Statistical methods

The significance of changes in various measured and derived quantities between different stages of pregnancy was estimated using student's t test on paired data.

Model of body composition

From the data given by Hytten and Leitch (1971), the increase of weight, water and potassium due to the fetus, placenta and amniotic fluid and to the increased volumes of the uterus and the maternal plasma and red cells, can be estimated (Table I). By subtracting these from our observed values, we obtained estimates for the maternal body; that is, maternal body mass ($\mathrm{BM_m}$), total body water ($\mathrm{TBW_m}$) and total body potassium ($\mathrm{TBK_m}$). The subscript m is used to denote that the values refer to the maternal body only.

Fat free mass ($\mathrm{FFM_m}$) for the first (10 to 14 weeks) and fourth (postpartum) measurements was calculated from:

$$\mathrm{FFM_m} = \mathrm{TBK_m}/60\ (\mathrm{kg})$$

The value of 60 mmol K/kg FFM, considered the most appropriate for use with our group of subjects, was estimated from published data (Womersley *et al*, 1972; Boddy *et al*, 1972; Boddy *et al*, 1973; Womersley *et al*, 1976). The expected amount of water associated with this $\mathrm{FFM_m}$ was calculated using a value of 0·73 kg water/kg FFM (Pace and Rathbun, 1945; Widdowson *et al*, 1951; Flanagan *et al*, 1966; Muldowney and Healy, 1967; Novak, 1967; Womersley *et al*, 1972). Excess water ($\mathrm{EW_m}$), used here to mean the mass of water in the maternal body which exceeds that normally associated with the $\mathrm{FFM_m}$, was then equal to the difference between the expected amount of water and $\mathrm{TBW_m}$. Maternal body fat ($\mathrm{BF_m}$) was then calculated thus:

$$\mathrm{BF_m} = \mathrm{BM_m} - (\mathrm{FFM_m} + \mathrm{EW_m})$$

TABLE I

*Contributions of various components to total body weight, water and potassium during pregnancy**

	Weight (kg)			Water (kg)			K (mmol)		
	1	2	3	1	2	3	1	2	3
Fetus	0·014	0·86	2·85	0·013	0·72	2·11	0·5	38·4	140·7
Placenta	0·10	0·26	0·58	0·09	0·22	0·48	4·3	11·3	25·3
Amniotic fluid	0·05	0·40	0·80	0·05	0·40	0·79	0·2	1·6	3·2
Uterus	0·16	0·65	0·90	0·133	0·54	0·75	8·3	33·6	46·5
Plasma	0·1	0·95	1·15	0·092	0·87	1·06	0·4	3·8	4·6
Red cells	0	0·11	0·22	0	0·07	0·14	0	10·5	21·0
Total	0·424	3·25	6·50	0·378	2·82	5·33	13·7	99·2	241·3

* Measurements periods (in weeks): 1 = 10 to 14; 2 = 24 to 28; 3 = 36 to 38.

The value 60 mmol K/kg FFM given above refers to the whole-body relationship, but when increments of body potassium and weight are considered this value is inappropriate. Therefore, for the measurements at the second (24 to 28 weeks) and third (36 to 38 weeks) periods during pregnancy, in calculating the changes in the lean tissue of the maternal body we have used the concentrations of 92 mmol K/kg and 0·79 kg water/kg increment in lean tissue. As we are uncertain of the precise cellular composition of the tissues undergoing hypertrophy and hyperplasia during pregnancy we have used these values based on skeletal muscle analyses (Widdowson and Dickerson, 1964). Increments of lean tissue so calculated, and amounts of water associated with them, were added to the values estimated for the FFM_m at the first measurement (10 to 14 weeks); EW_m and BF_m in these two periods were then calculated as above.

RESULTS

Changes in BM, TBK and TBW

Details of body weight (BM), total body potassium (TBK) and total body water (TBW) measured during pregnancy and postpartum in 27 subjects are given in Table II, and the mean values at each measurement period are shown in Table III. The mean increase in body weight between the first and third measurements (12 to 37 weeks) was 10·4±0·53 (SEM) kg with the major increase (6·08 kg) occurring between the first and second measurements (12 to 26 weeks). The maximum observed increase in weight was 15·65 kg. There was no significant difference ($p > 0·1$) between body weight measured at 10 to 14 weeks of pregnancy and at 6 to 15 weeks postpartum (mean difference 0·1±0·4 (SEM) kg). TBK increased on average by 312±25 (SEM) mmol between 12 and 37 weeks gestation with the larger increase (191±24 (SEM) mmol) occurring in the second period of measurement (26 to 37 weeks). The mean changes in TBK during pregnancy were all statistically highly significant ($p < 0·001$). There was a mean net residue of 40±29 (SEM) mmol K at the postpartum measurement compared with the first measurement in early pregnancy (10 to 14 weeks) but this difference was not statistically significant ($p > 0·1$). Total body water increased by 7·2±0·48 (SEM) kg between 10 and 37 weeks of pregnancy, fairly equally divided between the two measurement periods. TBW values at the postpartum measurement were very similar to those at the first measurement in early pregnancy, the mean difference being only 0·05±0·44 (SEM) kg ($p > 0·1$). Values of BM, TBK and TBW observed at the first measurement during pregnancy (10 to 14 weeks) and at 6 to 15 weeks postpartum were compared with expected values (Table III), estimated as described above. There was no significant difference between observed and expected values of BM ($p > 0·1$); differences in TBK were barely significant at the first measurement ($p \simeq 0·05$) and not significant ($p > 0·1$) at the postpartum measurement; but observed values of TBW were significantly greater ($p < 0·001$) than expected values by 3·0 kg on both occasions.

Changes in FFM_m, EW_m and BF_m

Values of fat free mass, excess water and fat derived for the maternal body according to the above model are given in Table IV and mean values obtained at the four measurement periods are shown in Figure 1. All three parameters increased during pregnancy but there were clear differences in the patterns of change. Maternal body fat increased rapidly after the first measurement (10 to 14 weeks), reached its maximum observed value at 24 to 28 weeks, and thereafter fell slightly during the remainder of pregnancy. Increases in FFM_m and EW_m were delayed in relation to the increase in BF_m and maximum values of these components were observed at the third measurement in late pregnancy (36 to 38 weeks). After delivery (6 to 15 weeks post partum), BF_m and EW_m fell to values which were similar on average to those measured in early pregnancy (10 to 14 weeks) but FFM_m remained elevated. The changes between measurements in lean tissue, excess water and fat of the maternal body are shown in Figure 2. Between 12 and 26 weeks of pregnancy, maternal fat increased by 2·4±0·53 (SEM) kg ($p < 0·001$) but small observed increments in lean tissue (0·38 kg) and excess water (0·49 kg) were not statistically significant ($p > 0·1$). Comparison between the first (10 to 14 weeks) and third (36 to 38 weeks) measurements showed significant increases in all three components, namely 0·92 kg lean tissue ($p < 0·01$), 1·54 kg excess water ($p < 0·01$) and

TABLE II

*Age, height, body weight, total body water, total body potassium, skinfold thickness and mean fat cell diameter at various times in normal pregnancy**

Patient	Age	Height (cm)	Body weight (kg)				Total body water (kg)				Total body potassium (mmol)				Skinfold thickness (mm)				Mean fat cell diameter (µm)				Weight of baby (kg)
			1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4	
1	19	160	61·0	66·8	71·4	—	32·6	35·4	38·7	—	2573	2765	2898	—	64·0	51·1	70·6	—	98	106	112	—	3·40
2	35	159	50·2	54·3	56·2	50·9	29·6	36·1	36·5	33·8	2376	2598	2519	2621	34·0	27·2	32·9	35·2	99	96	84	100	3·09
3	25	164	53·4	59·7	66·6	54·1	30·9	33·0	39·3	28·6	2396	2437	2757	2501	35·5	37·1	58·2	33·8	97	94	93	100	3·84
4	40	154	58·1	63·9	66·6	58·8	28·0	31·7	35·4	27·0	2238	2353	2501	2430	67·0	76·1	72·9	63·5	103	106	107	96	2·86
5	30	166	59·2	67·2	72·3	61·5	32·4	36·0	41·4	30·6	2509	2598	2916	2496	56·0	66·2	67·6	50·9	88	106	109	99	3·85
6	25	165	57·4	64·9	70·2	58·7	33·7	35·7	40·3	32·9	2519	2668	2862	2647	40·5	50·2	58·9	49·0	82	102	103	100	3·62
7	31	156	51·4	57·3	58·2	49·4	29·0	31·0	34·0	25·8	2228	2174	2174	2015	39·5	50·9	51·6	38·6	92	101	99	102	3·12
8	26	169	60·1	61·9	66·4	58·6	34·8	36·6	38·6	33·9	2619	2811	3036	2790	45·0	40·9	43·2	34·8	80	101	93	102	3·03
9	35	153	57·6	61·5	67·2	53·9	32·7	35·9	38·4	29·4	2274	2499	2701	2202	45·5	50·6	52·5	42·9	92	104	98	96	3·47
10	28	174	65·3	73·6	80·4	67·3	36·7	39·7	46·2	38·6	2836	2790	3184	2816	60·0	74·9	74·6	61·9	98	110	98	92	4·00
11	26	163	48·4	52·2	58·8	51·1	29·4	32·8	34·4	26·3	2322	2256	2519	2266	31·0	44·5	48·8	44·8	90	94	99	104	3·12
12	26	171	61·8	72·8	76·7	57·9	34·7	39·6	42·2	35·2	2639	2997	3046	2693	43·5	51·1	64·1	25·5	—	97	115	95	3·01
13	25	159	53·7	57·8	61·4	51·5	28·8	30·6	35·6	27·7	2084	2386	2343	2102	55·5	66·5	71·5	48·9	88	112	95	97	3·05
14	24	160	56·8	65·4	69·2	57·6	32·8	33·3	41·0	31·8	2389	2486	2816	2427	47·8	74·4	59·1	59·2	96	105	107	106	3·72
15	28	152	47·9	53·5	55·8	45·4	27·1	28·9	29·6	26·4	2041	2182	2251	1870	49·2	62·2	54·1	41·5	86	102	102	92	3·45
16	29	160	60·0	65·4	70·0	59·6	30·7	36·5	36·2	33·4	2442	2619	2770	2619	59·6	73·6	65·2	55·2	97	113	109	106	3·64
17	34	161	65·7	70·6	77·6	68·0	31·5	36·9	45·4	35·8	2519	2624	2959	2864	72·2	80·2	67·3	76·6	112	99	113	105	3·18
18	29	154	50·7	55·1	57·0	53·5	28·0	33·4	34·3	29·6	2125	2281	2437	2391	42·2	56·1	60·5	65·9	89	96	99	99	2·94
19	26	156	56·2	63·7	65·7	55·5	31·0	34·0	38·0	29·7	2327	2478	2806	2437	58·6	55·8	52·7	43·8	103	102	101	102	3·32
20	29	167	56·9	63·7	66·6	57·0	33·2	32·3	38·6	33·6	2478	2596	2824	2238	44·2	55·9	53·6	43·7	98	103	109	98	3·82
21	29	157	61·9	68·4	72·8	64·9	35·9	38·1	41·0	35·6	2652	2696	2928	2625	48·9	65·9	66·6	51·9	96	102	94	103	3·56
22	28	164	56·5	62·1	65·3	55·2	30·1	33·2	35·9	31·5	2210	2294	2376	2281	39·8	49·1	50·3	34·9	104	103	100	100	3·20
23	24	161	52·5	55·2	63·9	54·6	29·6	32·8	39·6	32·5	2379	2320	2614	2445	49·6	46·9	48·5	46·2	97	95	100	95	3·54
24	26	164	56·5	61·1	65·3	54·2	29·8	34·7	37·2	28·5	2496	2327	2647	2279	43·2	51·3	46·1	32·6	104	106	106	104	3·74
25	26	166	63·6	72·8	75·6	64·6	36·9	41·3	47·6	35·4	2964	3018	3210	2916	49·6	56·6	58·8	44·9	103	99	106	98	4·25
26	29	168	69·8	76·4	80·4	70·0	35·5	38·6	42·4	38·9	2824	3072	3176	2841	60·4	82·2	85·5	80·6	98	99	112	101	3·08
27	20	158	59·5	68·9	75·1	59·2	34·2	38·7	46·3	33·5	2496	2885	3105	2601	58·9	59·9	73·0	49·0	102	107	109	109	4·24
Mean	28	162	57·5	63·5	67·9	57·4	31·8	35·1	39·0	31·8	2442	2563	2754	2478	48·6	57·7	59·6	48·3	96	102	103	100	3·45
SD	4	6	5·4	6·6	7·1	6·0	2·8	3·1	4·2	3·7	226	257	292	271	10·2	13·6	11·5	13·4	7	5	7	4	0·39

* Measurement periods (in weeks): 1 = 10 to 14; 2 = 24 to 28; 3 = 36 to 38; 4 = post partum.

TABLE III

Body weight, total body potassium (TBK) and total body water (TBW) measured in 27 subjects, on three occasions during pregnancy and post partum. Expected values are shown for the first and fourth measurements

Measurement period (weeks)	Body weight (kg) Mean ± SEM	TBK (mmol) Mean ± SEM	TBW (kg) Mean ± SEM
10–14 (n = 27) expected values	57·45 ± 1·04 57·6 ± 0·7	2442 ± 43 2492 ± 37	31·83 ± 0·54 28·81 ± 0·40
24–28 (n = 27)	63·54 ± 1·27	2563 ± 49	35·07 ± 0·59
36–38 (n = 27)	67·85 ± 1·38	2754 ± 56	39·04 ± 0·82
post partum (n = 26) expected values	57·41 ± 1·18 57·8 ± 0·7	2478 ± 53 2484 ± 38	31·75 ± 0·73 28·79 ± 0·44

TABLE IV

*Derived values of fat free mass, excess water and fat at various times in normal pregnancy**

	Fat free mass (kg)				Excess water (kg)				Fat (kg)			
Patient	1	2	3	4	1	2	3	4	1	2	3	4
1	42·65	43·81	43·71	–	1·05	0·51	1·35	–	16·88	19·25	19·84	–
2	39·37	40·86	38·46	43·69	0·48	3·36	3·10	1·95	9·89	6·80	8·09	5·26
3	39·71	39·23	41·16	41·69	1·53	1·57	3·87	−1·84	11·69	15·62	15·07	14·20
4	37·07	37·40	37·47	40·49	0·51	1·52	2·71	−2·54	20·05	21·70	19·87	20·80
5	41·58	41·63	43·53	41·60	1·62	2·77	4·13	0·20	15·53	19·52	18·09	19·69
6	41·75	42·44	43·01	44·12	2·85	1·83	3·49	0·71	12·33	17·35	17·15	13·85
7	36·90	35·39	33·85	33·59	1·66	2·47	4·19	1·24	12·37	16·16	13·66	14·56
8	43·42	44·58	45·48	46·50	2·76	1·20	−0·06	−0·07	13·45	12·48	14·43	12·12
9	36·66	39·18	39·83	36·70	4·82	4·39	3·91	2·64	14·65	14·65	16·96	14·56
10	47·04	45·62	48·36	46·93	1·95	3·64	5·51	4·32	15·84	21·06	19·98	16·08
11	38·47	36·82	38·14	37·77	0·90	3·20	1·29	−1·30	8·56	8·90	12·82	14·63
12	43·76	46·73	45·72	44·88	2·39	2·50	3·41	2·41	15·18	20·34	21·07	10·61
13	34·51	36·87	34·85	35·04	3·18	0·71	4·84	2·14	15·54	16·99	15·16	14·27
14	39·58	39·71	41·75	40·45	3·54	1·46	5·05	2·30	13·21	20·95	15·85	14·85
15	33·78	34·38	33·59	31·16	2·08	0·92	−0·23	3·66	11·57	14·92	15·89	10·58
16	40·48	41·47	41·57	43·65	0·80	3·35	0·47	1·54	18·25	17·35	21·46	14·41
17	41·75	41·97	44·07	47·74	0·60	3·45	7·73	0·99	22·88	21·95	19·30	19·22
18	35·19	35·96	36·11	39·86	1·97	4·28	2·52	0·53	13·07	11·63	11·87	13·10
19	38·56	39·28	41·30	40·62	2·47	2·47	2·36	0·00	14·75	18·72	15·49	14·83
20	41·07	41·42	42·35	37·30	2·86	−0·83	2·25	5·75	12·55	19·88	15·45	13·94
21	43·97	43·52	44·51	43·73	3·46	3·52	3·10	3·70	14·05	18·13	18·69	17·47
22	36·60	36·59	35·94	38·02	3·03	3·62	4·33	3·73	16·45	18·61	18·53	13·45
23	39·41	37·85	39·50	40·75	0·41	2·44	5·41	2·76	12·26	11·63	12·44	11·09
24	41·37	38·61	40·54	37·98	−0·61	3·87	2·33	0·81	15·48	15·39	15·93	15·41
25	49·17	48·83	49·37	48·59	0·64	2·84	6·24	−0·06	13·32	17·90	13·49	16·07
26	46·83	48·60	48·20	47·36	0·90	0·17	1·81	4·36	21·65	24·40	23·84	18·28
27	41·37	44·67	45·52	43·35	3·58	3·08	7·51	1·84	14·08	17·87	15·57	14·01
Mean	40·48	40·87	41·40	41·29	1·90	2·38	3·43	1·61	14·65	17·06	16·52	14·51
SD	3·77	3·98	4·39	4·51	1·29	1·34	2·05	2·00	3·27	4·08	3·43	3·20

* Measurement periods (in weeks): 1 = 10 to 14; 2 = 24 to 28; 3 = 36 to 38; 4 = post partum.

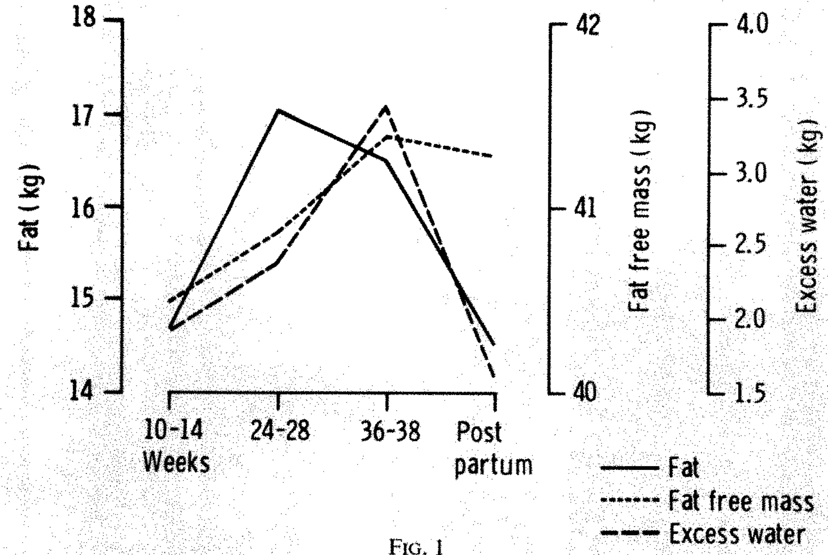

FIG. 1

Changes in fat, fat-free mass and excess water of the maternal body during normal pregnancy.

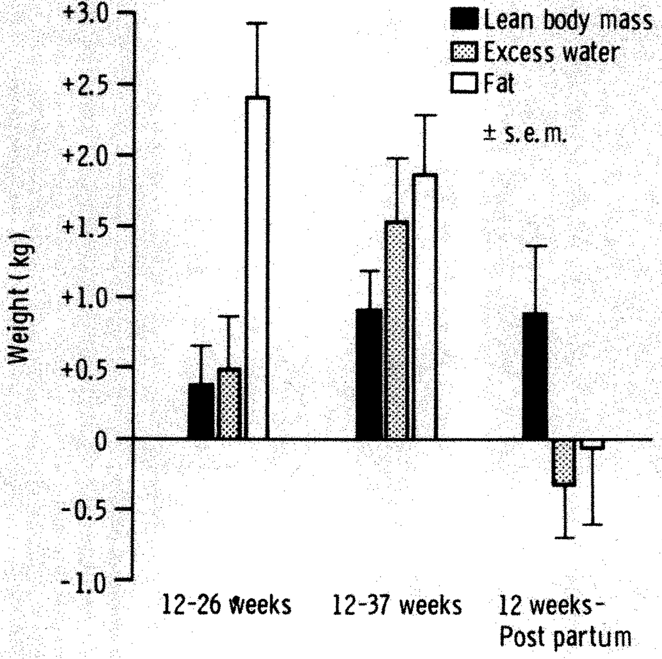

FIG. 2

Changes in fat, lean tissue and excess water of the maternal body which occur in different periods of normal pregnancy, (a) between 12 and 26 weeks gestation; (b) between 12 and 37 weeks gestation; (c) between 12 weeks gestation and post partum.

1·87 kg fat ($p<0·001$). Clearly there was no significant net accumulation of fat during the last three months of pregnancy. There was in fact an apparent loss of 0·54 kg fat on average during this period, but this change was not statistically significant ($p>0·1$). In the same period, however, further increases of 0·54 kg lean tissue and 1·05 kg excess water were just significant ($p<0·05$). Measurements at 6 to 15 weeks post partum indicated very small net losses of 0·05 kg fat and 0·32 kg excess water when compared with the first measurement in pregnancy (10 to 14 weeks), neither of which were significant ($p>0·1$). A larger difference in lean tissue estimates between these measurements, indicating a net increase of 0·89 kg, was also not statistically significant ($p>0·05$).

Skinfold measurements and fat cell size

Skinfold values (sum of readings at four sites) and fat cell sizes during and after pregnancy are given in Table II. Mean values at each of the four measurements are shown in Figure 3, which also includes the mean maternal fat values for comparison of patterns of change. Both skinfolds and fat cell diameter increased rapidly between 12 and 26 weeks similar to body fat. There was little subsequent change during pregnancy in fat cell diameter, whereas the mean skinfold value rose slightly to a peak at 37 weeks despite the fact that the mean value fell during this period. Skinfold thickness fell after delivery to a mean value which was not significantly different ($p>0·1$) from that obtained at 10 to 14 weeks pregnancy. Fat cell diameter, although falling after delivery, on average remained significantly higher ($p<0·01$) at the postpartum measurement.

Using formulae given by Durnin and Womersley (1974), skinfold thickness can be used to estimate the amount of body fat. This was done for each of the four measurement periods (Table V) and the results compared with fat values estimated using the maternal body model described above. Regressions of fat values estimated by both methods are shown in Figure 4. Correlation coefficients for the measurement periods 1 to 4 were 0·88, 0·88, 0·79 and 0·71 respectively with standard deviations from regression of 1·6, 2·0, 2·1 and 2·3 kg fat.

There was poor correlation between mean fat cell size and maternal body fat estimated using the present model. The correlation coefficients for the measurement periods 1 to 4 being 0·5, 0·45, 0·65 and 0·17 respectively.

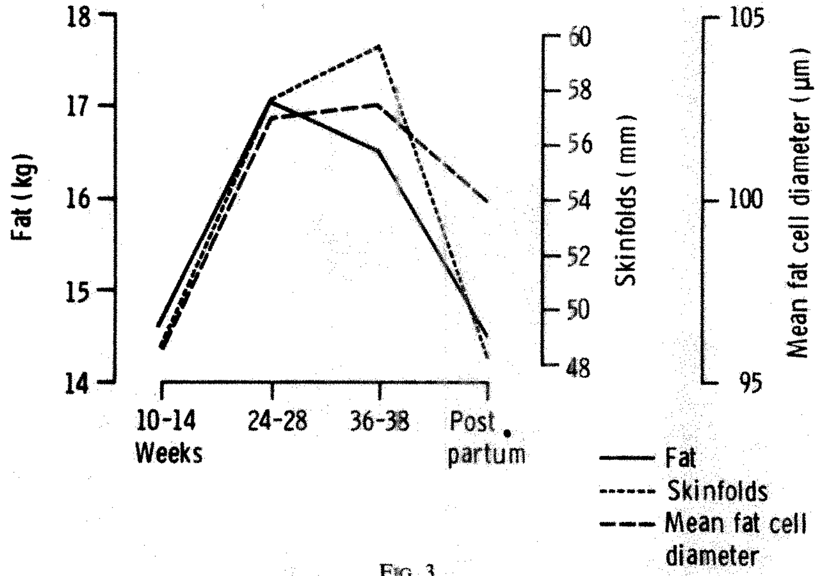

FIG. 3

Changes in skinfold thickness and mean fat cell diameter in relation to changes in fat of the maternal body during normal pregnancy.

TABLE V

Values of body fat estimated from skinfold thickness at various periods of normal pregnancy

	Measurement period			
	1	2	3	4
Mean (kg)	15·4	17·5	18·2	15·2
SD	2·9	3·6	3·5	3·6
n	27	27	27	26

Measurement periods (in weeks): 1 = 10 to 14; 2 = 24 to 28; 3 = 36 to 38; 4 = post partum.

DISCUSSION

The combination of serial measurements of body weight (BM), total body potassium (TBK) and total body water (TBW) during normal pregnancy has not previously been reported for a comparable group. The incorporation of TBK measurements permits a more detailed analysis of the composition of changes in body weight than previous studies based only on BM and TBW changes. In association with the above body composition model, our combination of measurements, after correction for the contributions due to changes associated with the developing fetus, allows estimates to be made of the changes in the maternal body components, namely fat free mass (FFM_m) excess water (EW_m) and fat (BF_m) during pregnancy. TBK is almost entirely located in the FFM, with relatively constant concentration in normal subjects, and its measurement therefore provided the initial step in the analysis of changes in BM into separate components. Serial measurements of TBK can now be made reliably by the application of sensitive whole-body counters. A change in TBW of the maternal body results from increased lean tissue but also from any increase in excess interstitial water. Observed changes in TBW measurements alone, therefore,

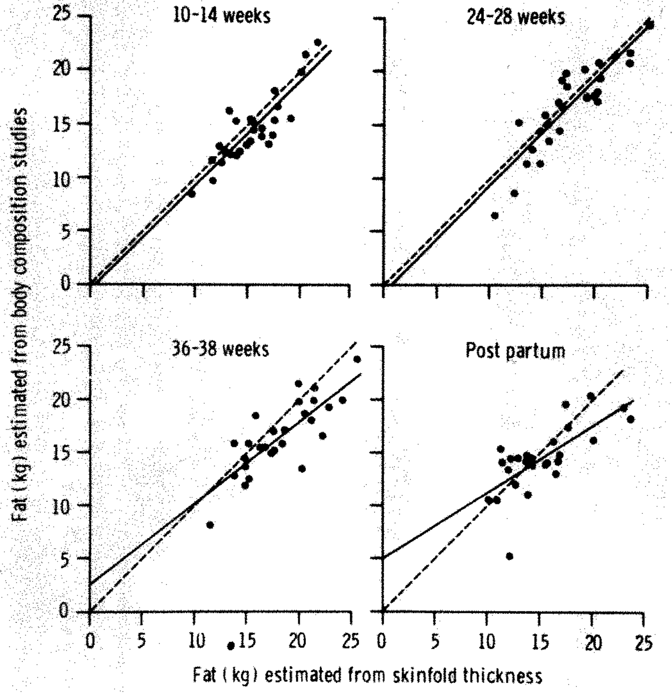

FIG. 4

Regressions of maternal body fat values derived using the body composition model or estimated from skinfold thickness at various times during normal pregnancy. (a) 10 to 14 weeks; (b) 24 to 28 weeks; (c) 36 to 38 weeks; (d) 6 to 15 weeks postpartum. Regression lines (solid) and lines of identity (dashed) are indicated.

cannot uniquely define these two components but, after estimation of FFM from TBK measurements, they permit the estimation of the amount of excess water. This is possible because the water content of FFM is also relatively constant in normal subjects. It is then a simple matter to estimate body fat by difference. The combination of measurements used in the present study to estimate the amount of maternal body fat provides a simpler and more convenient method than techniques based on direct determination of body density.

Changes in measured quantities during pregnancy

The results shown in Table III indicate that, between 12 and 37 weeks of normal pregnancy, mean increases of 10·4 (±2·7 (SD)) kg body weight and 7·2 (±2·5 (SD)) kg body water occurred and that at 6 to 15 weeks post partum, body weight and TBW had, on average, each returned to within 0·1 kg of their values at 10 to 14 weeks gestation. These results are similar to those observed by Hytten *et al* (1966) in a large (n = 93) linear series, except that the latter authors found a mean net increase of 1·94 kg body weight between the 10 week and postpartum measurements. We observed an average increase in total body potassium of 312 mmol between 12 and 37 weeks gestation which had almost completely disappeared at the postpartum measurement. This gain in TBK was similar to that estimated by Godfrey and Wadsworth (1970) after adjustment of their observed values for the effects of variable whole-body counting efficiency due to physiological changes at different stages of pregnancy. Our TBK results were also in reasonable agreement with other values inferred where possible from very limited data (Emerson *et al*, 1975; King *et al*, 1973; MacGillivray and Buchanan, 1958).

Although the general pattern of variation in skinfold thickness (sum of measurements at four sites) is similar to that which can be deduced from the data of Taggart *et al* (1967), the magnitudes of absolute measurements and changes were different. Our mean values were about 20 per cent greater, the measurements at the suprailiac site accounting for almost all this difference. As far as we are aware, serial measurements of fat cell diameter have not previously been made during pregnancy.

Changes in derived quantities during pregnancy

Application of our body composition model to the measurement data indicates that, on average, an increment of 0·9 kg lean tissue occurred in the maternal body during the last two trimesters. This increment can be partly accounted for by increased mammary tissue. The weight gain of mammary gland during pregnancy is about 0·4 kg of which 0·3 kg is water (Hytten and Leitch, 1971), the increase at 10 weeks being only 10 per cent of this. The potassium content of mammary gland is not known, but the latter authors used a value of 51 mmol/kg, similar to that of average viscera, which is considerably less than the value used for incremental lean tissue in our model. Although our results therefore suggest that other components of the maternal fat free body have increased by at least 0·5 kg during pregnancy, this increment is close to the limits of significance.

The model further indicates that the excess water of the maternal body increased by 1·5 kg between 12 and 37 weeks gestation and, in the postpartum period, returned to a mean value only 0·3 kg lower than the early measurement in pregnancy (10 to 14 weeks). The observed increase of 1·5 kg excess water between 12 and 37 weeks gestation was similar to the value of 1·68 kg estimated between 10 and 40 weeks in patients with minimal oedema by Hytten and Leitch (1971).

Results relating to maternal fat stores also corroborate the conclusions of Hytten and Leitch (1971), who inferred increases in maternal fat of up to 3·5 kg at 30 weeks gestation. Interpolation of their data shows that between weeks 12 and 26, the mean times of our first and second measurements, the increase in maternal fat was 2·3 kg, in close agreement with our value of 2·4 kg (Fig. 2). Since we did not make measurements at 30 weeks, it is possible that we did not observe the maximum fat increase, and in the last trimester our results show a net deficit of about 0·5 kg fat. In the equivalent period, the conclusions of Hytten and Leitch (1971) depended on whether patients had minimal or generalized oedema: maternal fat stores remained fairly constant in the former category during the last trimester but diminished in the latter by about 0·8 kg. For various reasons it is difficult to compare our results of changes in fat deposition with those from other studies. The study by Seitchik (1967) was based on a randomized series of 126 patients, not on a linear series of the same patients measured repeatedly throughout pregnancy. The data, therefore, cannot be used to determine the effect of pregnancy on changes in measured parameters and this presumably accounts for an apparently inconsistent trend in the amount of fat, expressed as a proportion of body weight. The findings of Emerson *et al* (1975) cannot be compared with ours because their patients were investigated in an artificial environment created by dietary restriction. Moreover, only five normal patients were studied and measurements were not started until 16 or 20 weeks gestation.

Although the mean changes we observed in fat cell diameter follow the pattern of total body fat deposition, there is poor correlation between individual total body fat and mean fat cell diameter measurements at each of the four occasions the patients were investigated. It is possible that changes observed in fat cells obtained from the buttock are not representative of the overall changes occurring in subcutaneous fat in pregnancy. A more representative pattern may have been seen in fat cells obtained by biopsy from multiple sites. This technique also fails to account for changes occurring in the internal fat depots and emphasizes the difficulties in drawing conclusions regarding total body fat changes from measurements of fat cell diameter alone (Jung *et al*, 1978). It is not possible to authoritatively dismiss the theory that fat accumulation can be accounted for by adipocyte hypercellularity because we did not measure fat cell numbers. It is, however, apparent from our observations on the changes in fat cell diameter that the fat cell is capable of storing pure lipid in much greater quantity during pregnancy.

The pattern of the changes in the total skinfolds was found to differ in late pregnancy from that of total body fat. The peak skinfold thickness was observed towards the end of the third trimester (36 to 38 weeks), unlike total body fat which reached a peak at the end of the second trimester (24 to 28 weeks). This difference in pattern may be due to the accumulation of water in the subcutaneous tissue in late pregnancy and was particularly noticeable in the suprailiac skinfold measurement. Body fat calculated from skinfold thickness showed good correlation with those levels of body fat calculated by measurement of total body water and potassium, particularly in early and mid-pregnancy. Correlations in late pregnancy and the puerperium were less good. The water excess very likely accounts for this in late pregnancy but in the puerperium where the total skinfolds had reverted to the early pregnancy level (10 to 14 weeks), the reason for the poorer correlation is not clear.

In conclusion, the results of the investigation described show that the general trend for fat deposition in pregnancy is that of an accumulation of fat reserve during the second trimester. Thereafter there is apparently no further net accumulation of fat during the last trimester. In the puerperium, total body fat diminishes, decreasing to the early pregnancy levels. This pattern of fat deposition corresponds with that inferred from measurements of body weight and body composition by Thomson and Hytten (1961) and Hytten and Leitch (1971). Our findings support their hypothesis that fat is accumulated in pregnancy and may act as a nutrient reserve during times of food deprivation.

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INTRAPARTUM FETAL MONITORING WITH THE CEREBRAL FUNCTION MONITOR

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Summary

We report a trial of the technical feasibility of monitoring the state of the fetal brain during labour using the Cerebral Function Monitor (CFM). This device was developed for long-term monitoring of the electroencephalogram (EEG). A tripolar scalp electrode allows removal of the fetal electrocardiograph (ECG) from the fetal EEG. Technically satisfactory recordings were obtained from 15 fetuses during labour for periods of up to 6½ hours before delivery. There were alterations of CFM trace with fetal distress and also during general anaesthesia for Caesarean section.

THE aim of intrapartum fetal monitoring is to prevent fetal morbidity and mortality, particularly neurological impairment, arising from hypoxia. The recording of fetal electroencephalograms (EEGs) is the only available method for monitoring the state of the fetal brain during labour. It has been extensively investigated and its validity established (Rosen *et al*, 1973*a* and *b*; Sokol and Rosen, 1974). Chik *et al* (1976), by computer analysis of fetal EEG patterns, obtained a significant difference ($p < 0{\cdot}001$) between 11 normal babies and 9 found to be neurologically abnormal at one year. A discriminant analysis of the fetal EEG correctly predicted outcome in 16 of these.

For fetal EEG to be used as a routine method for monitoring fetal wellbeing during labour (Chachava, 1976) several problems must be overcome: fetal EEG recordings are subject to artefactual contamination, principally from the fetal electrocardiogram (ECG), fetal and maternal movement, and fetal scalp muscle activity; the paper speed is such that 108 m/hour are used; the apparatus, technical assistance and materials are expensive and continuous expert interpretation is required. Consequently fetal EEG monitoring is currently only a research technique (Sokol and Rosen, 1974).

In contrast the Cerebral Function Monitor (CFM, Lectromed Limited, Jersey, Channel Islands), developed for long term EEG monitoring (Maynard *et al*, 1969), produces a record of EEG amplitude variations at a rate of 6 or 30 cm/hour. Most artefacts are either eliminated or separately indicated. The CFM is relatively inexpensive, no great skill is required to operate the machine and the tracings are generally easy to interpret. It has, for example, been used extensively to indicate the existence of adequate cerebral perfusion during cardio-pulmonary by-pass (Schwartz *et al*, 1973; Branthwaite, 1973 and 1975). In addition, the CFM has been employed to determine optimal rates for the administration of anaesthesia (Dubois *et al*, 1978).

We now report the results of a trial of the technical feasibility of routinely monitoring the fetal EEG during labour with the CFM.

METHOD

To obtain reliable CFM tracings it was necessary to minimise in the fetal EEG artefacts caused by the fetal ECG, fetal and maternal movement, and fetal scalp muscle activity. The fetal ECG was removed by means of a subtraction technique using signals from three electrodes housed within a small cup held to the fetal scalp by a light suction (Fig. 1; Maynard, 1979). Voltages arising from fetal and maternal movements causing variations of electrode contact pressure were reduced by employing large surface area electrodes which also mini-

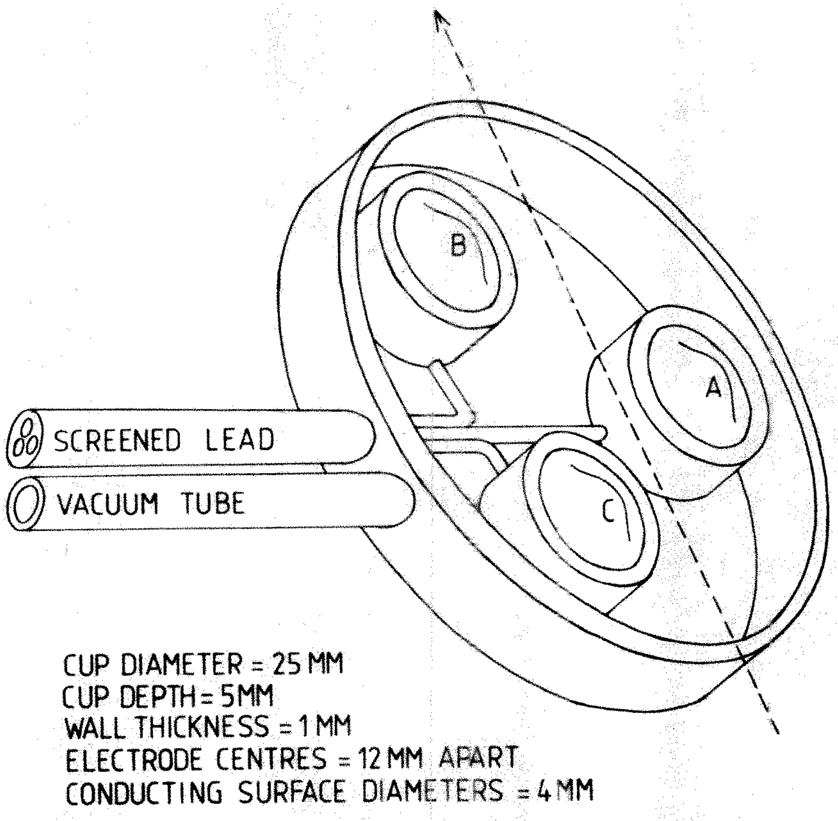

FIG. 1

Fetal electrode: The electrode cup is made from electrically insulating material such as perspex. Each electrode, made from dental amalgam or silver and with a slightly domed or conical rough surface for maximum contact area, is contained within an insulating cylinder. The cylinder, when pressed to the scalp, helps to isolate the electrode from the surrounding medium.

Principle of operation: If the dotted arrow represents the direction of the ECG potential gradient, then the ECG potential difference between B and C (V_{BC}) is proportional to the distance between the perpendicular projections of B and C onto the arrow. The potential difference between A and C (V_{AC}) will be less than V_{BC}. Therefore V_{BC} can be divided and subtracted from V_{AC} to remove the ECG potential. Since EEG potential gradients continually vary in direction, EEG potentials are not reduced to zero. Different directions of the ECG gradient can be accommodated by selecting the appropriate pairs of electrodes.

UK and USA patents applied for.

mised electrode contact impedance. Scalp muscle activity, which may contain energy at fetal EEG frequencies, is only partly eliminated by the CFM and so this activity was recorded on a second trace which also continuously monitored electrode impedance (see Fig. 3).

The sterilised suction cup electrode could be applied to the fetal head through a cervix which was 3 cm dilated and it was held in position by a vacuum of 80 cm water. The vacuum pump pressure regulator was designed to give a visible and audible indication of a satisfactory seal between fetal scalp and electrode. The unprocessed fetal EEG was obtained from the CFM after amplification and viewed on an oscilloscope. The fetal ECG was then balanced out (Figs. 1 and 2). Polygraphic tracings on a Devices MX4 recorder were obtained of the processed fetal EEG, electrode impedance, fetal heart rate (FHR, from a separate scalp electrode) and uterine contractions (from an abdominal transducer).

Recordings were made from 15 patients for periods of up to 6½ hours before delivery. The fetal EEG was also monitored intermittently on a conventional recorder in three patients to establish the reliability of the CFM trace. The procedure was explained to all patients and informed consent obtained. The traces obtained were not used to guide the management of labour.

RESULTS

On no occasion was there difficulty in balancing out the fetal ECG to an insignificant level. Rebalancing was sometimes necessary following maternal or fetal movements. The total amount of trace free of artefact was greater than 95 per cent for all recordings. Occasionally artefactual activity, which was not indicated on the impedance trace, was produced by trembling of the women's legs. Very slow seepage of fluid past the electrope cup rim and into the vacuum line sometimes occurred. It did not appear to affect the fetal EEG. A noticeable flow usually presaged detachment of the electrode cup from the fetal scalp.

Tracings obtained during labour are illustrated in Figures 3, 4 and 5. It proved possible on one occasion to monitor the effect on the fetal EEG of anaesthesia for Caesarean section (Fig. 6). In general, trends to a higher or lower CFM trace occurred both independently of, and in association with, contractions and both with and without changes of FHR pattern. Periodic alterations of CFM trace width (Fig. 4) indicative of sleep cycles, were occasionally seen. Transient changes of electrode impedance were sometimes

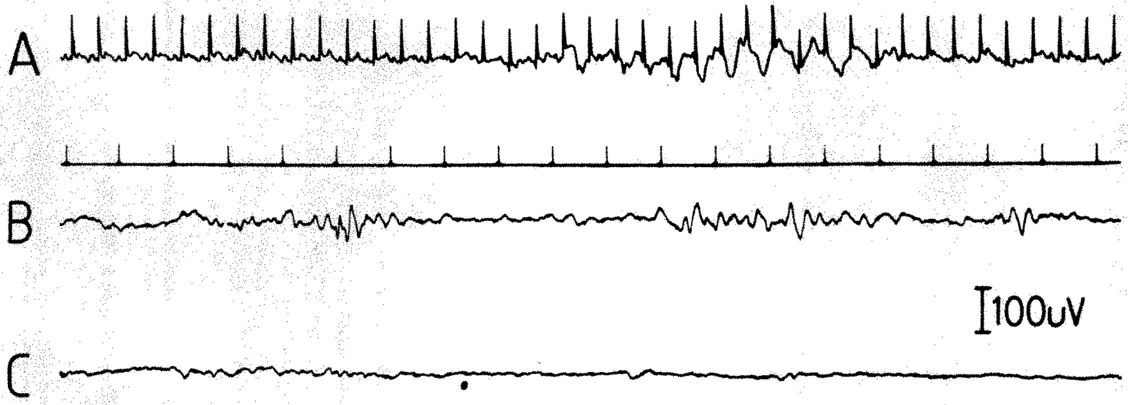

FIG. 2

Fetal EEG:

(A) Fetal EEG with superimposed fetal ECG. (B) Fetal EEG with fetal ECG removed. The alternation between medium and high amplitude fetal EEG produces a broad band CFM trace. This recording was made shortly after the beginning of the CFM record shown in Figure 4. (C) Low voltage fetal EEG taken from the end of the recording shown in Figure 4.

Time markers are at 1 second intervals.

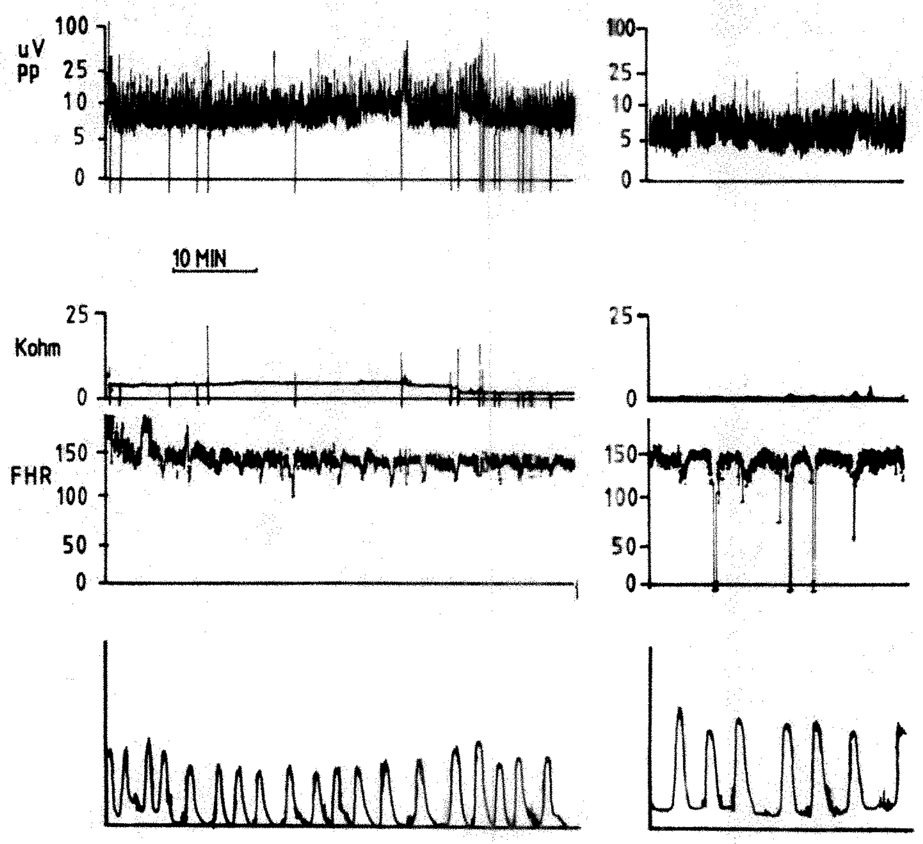

FIG. 3

Polygraphic recording indicating the extent of a slow fall of CFM amplitude that occurred during the last three hours of labour. The second section begins two hours after the first and ends 40 minutes before delivery.

From above down are shown:

(1) CFM output in microvolts peak to peak. The write out follows the smoothed (time constant 0·5 second) amplitude fluctuations of a filtered and rectified fetal EEG signal. Because the paper moves slowly a thick band of activity is written. The upper and lower edges of this band are related to the maximum and minimum voltages reached by the fetal EEG over short periods of time. (2) Electrode impedance in kilohms. Variations of impedance in this trace are caused by maternal movements. Electrode artefacts are indicated by excursions of the trace upwards or by cut-outs to below the baseline of both this and the CFM trace. No scalp muscle activity is indicated. Its presence would be shown by a thickening of the impedance trace. (3) Fetal heart rate showing type 1 dips with contractions. Occasional type 2 dips occurred in the last hour of labour. (4) Uterine contractions.

evident near the peaks of contractions, presumably caused by alteration of contact pressure. Shifts of CFM trace level, with or without accompanying step-like changes of electrode impedance, were frequently seen in association with alterations of maternal position (Fig. 5) and vaginal examinations.

The application of Keilland's forceps once produced a fall to a low level trace equivalent to the fetal EEG alteration reported by Rosen *et al* (1973*a*). In another record a fall to a predominantly baseline trace occurred one hour before delivery, even though a FHR around 140 with small type 1 dips was maintained.

DISCUSSION

These preliminary results indicate that routine monitoring of the fetal EEG with the CFM is

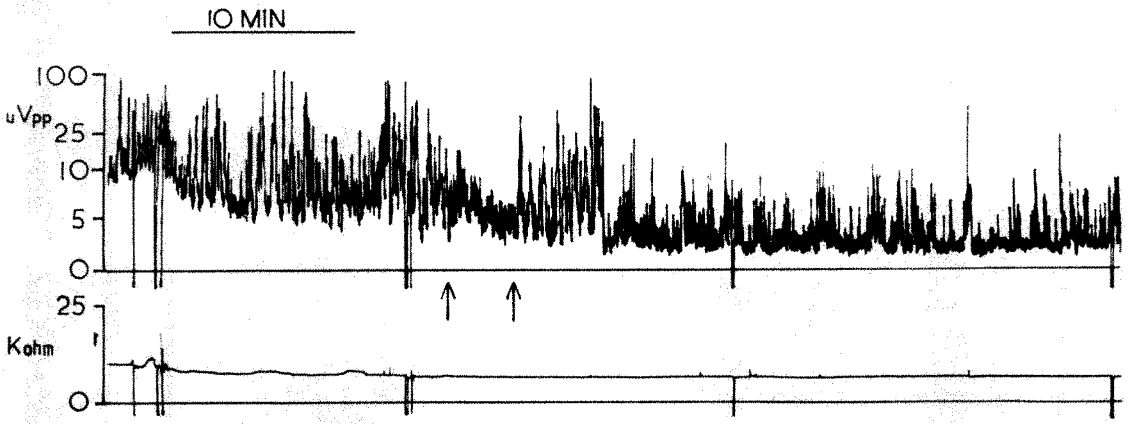

FIG. 4

Record showing fall of CFM trace to a low voltage which was then sustained until Caesarean section began 20 minutes after the end of this illustration. A few brief falls to a lower edge level of two microvolts had occurred some two hours earlier. Subsequently alterations of maternal position were associated with considerable fluctuation of average trace level. At the beginning of this illustration the fetal blood pH was 7·15. Previously the FHR had shown type 1 dips and then rose to around 185 where it remained except for three dips to 80, 70 and 100 between the two arrows. The infant was resuscitated with difficulty. Fetal EEG samples taken during this trace are shown in Figure 2B and 2C. The broad band trace immediately to the left and right of the arrows is typical of the 'tracé alternant' fetal EEG pattern shown in Figure 2B. 'Tracé alternant' may be associated with the quiet sleep phase of a fetal sleeping-waking cycle (Fargier *et al*, 1974; Zorn *et al*, 1974).

feasible. The technique of housing all three electrodes in one suction cup is clinically advantageous and gives standardised electrode spacing. The disadvantage of placing electrodes close together is that the recorded fetal EEG tends to be of low voltage. Fortunately the CFM is more sensitive and has a lower noise level than a conventional EEG recorder, the half scale deflection on a semi-logarithmic scale being 10 microvolts from peak to peak. Some technical improvement is still necessary; for example, the fetal ECG subtraction should be made automatic and the fetal ECG and fetal EEG electrodes should be incorporated in the same assembly (Rosen *et al*, 1970). Although Zorn *et al* (1974) have used an accelerometer to detect electrode movement, a means of indicating electrode pressure seems preferable (see Fig. 5).

During this study CFM changes indicative of sleep cycles were occasionally seen (see Fig. 4). Fargier *et al* (1974) consider that prolonged absence of such cycles indicates cerebral distress. However, the recognition of sleep cycles and the interpretation of fetal CFM traces will be complicated by changes of fetal EEG patterns with increasing gestational age (Sokol and Rosen, 1974). Fortunately EEG patterns in the fetus and newborn of the same maturity are similar (Fargier *et al*, 1974; Sokol and Rosen, 1974; Zorn *et al*, 1974; Borgstedt *et al*, 1975). Therefore, to help guide the interpretation of fetal CFM records according to gestational age, traces obtained from newborn are the subject of a separate study.

The ability to monitor the fetal EEGs during anaesthesia for Caesarean surgery may assist the refinement of anaesthetic technique. In Figure 6, the rise of the CFM trace to a peak at induction with a subsequent fall to a lower level is similar to that seen in adults (Dubois *et al*, 1978). However, if seen in an adult the continued depression of the trace would suggest excessive depth of anaesthesia. Non-anaesthetic drugs are also known to affect the fetal EEG (Rosen *et al*, 1970; Peltzman *et al*, 1973; Fargier *et al*, 1974) and the CFM may be of value in monitoring the effect of these.

In both neonatal and fetal EEGs, neurological damage has been correlated with a discontinuous EEG pattern, asymmetrics, seizure discharges, sharp waves and flattenings (Rose and Lombroso, 1970; Sokol *et al*, 1974; Borgstedt *et al*, 1975; Obrecht *et al*, 1977). Individual sharp waves and asymmetries would not be

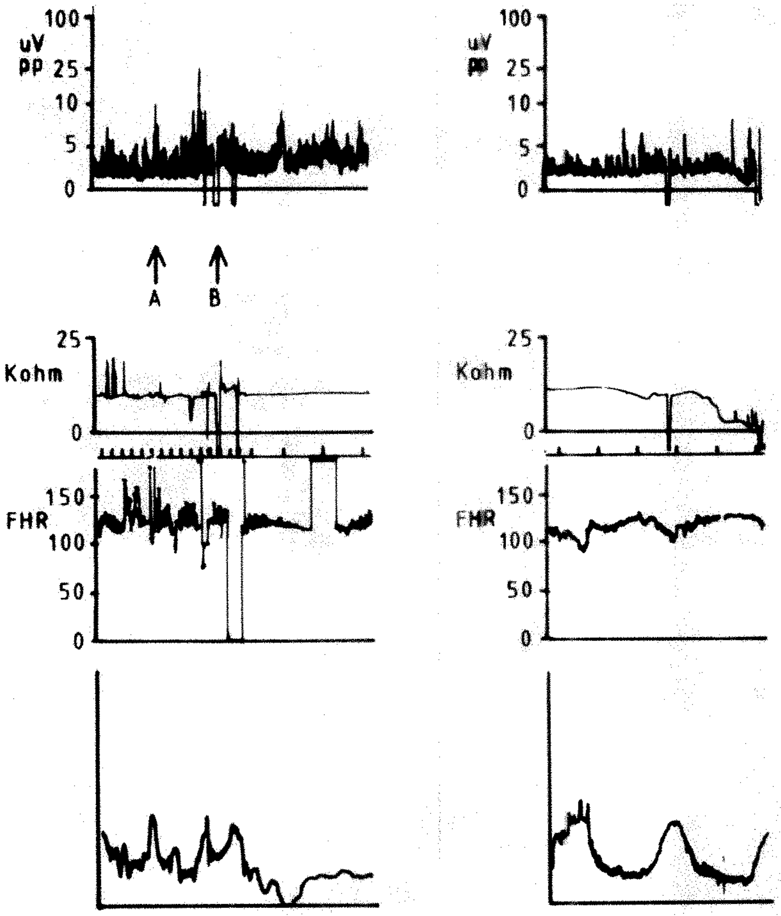

Fig. 5

The left hand CFM trace, taken during epidural anaesthesia, had fallen from a lower edge level of 5 microvolts over the preceding 12 minutes in a manner similar to Figure 4. At arrow A oxygen was given. At arrow B the patient was put into a 15° lateral tilt position. This was followed by a slight rise in the level of the tracing. The right hand trace begins 22 minutes after the first. It has less amplitude variability. A drop of impedance, possibly caused by an increase of electrode contact pressure, is followed some 20 seconds later by a slower decline in CFM amplitude. The minimum level is reached as the final contraction begins. Delivery by vacuum extraction followed immediately. The fetus was found to have its umbilical cord tightly around the neck. Time markers are at 1 minute intervals. Note the paper speed change in the left hand trace.

detected on the CFM trace, but seizure discharges (Prior *et al*, 1973) and flattenings are clearly visible.

Finally, the contrast between Figures 3, 4 and 5, illustrates how the CFM may prove valuable in indicating deterioration of normal fetal EEG in time for corrective action to be taken. In adults, falls of CFM trace to near the baseline similar to Figure 4 and also more rapid falls are indicative of inadequate cerebral perfusion (Prior, 1979), and CFM changes frequently give sufficiently early warning for the prevention of brain damage. The close relationship between features of CFM traces and neurological damage complicating cardiac surgery is discussed by Schwartz *et al* (1973) and Branthwaite (1973 and 1975). However, caution is necessary before applying to the fetus experience gained in adults

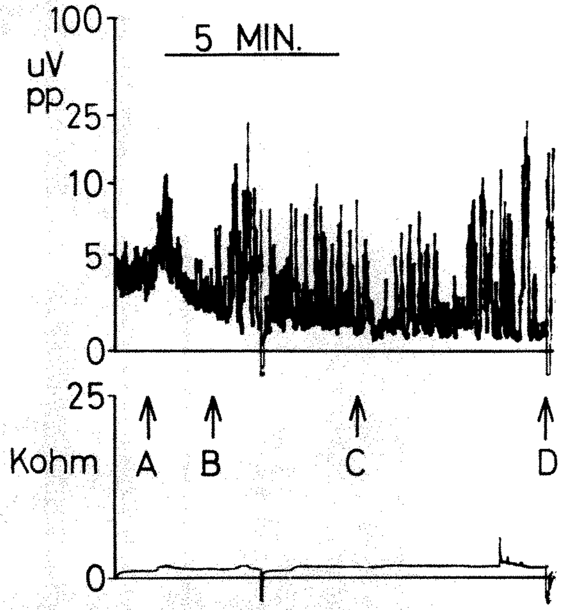

FIG. 6

Fetal CFM record obtained during anaesthesia for Caesarean section done for fetal bradycardia (FHR = 80) for one hour.
(A) Induction of anaesthesia: thiopentone 250 mg, suxamethonium 100 mg, nitrous oxide, oxygen 30 to 50 per cent. (B) Surgery begins. (C) Inspired oxygen reaches 50 per cent; trilene introduced at 0·1 per cent. (D) Delivery.

because of physiological and EEG differences. Therefore clinical trials to determine the relationship between fetal CFM patterns, other measures of fetal wellbeing, and neurological outcome, are in progress.

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MEASUREMENT OF FETAL TRANSCUTANEOUS OXYGEN TENSION—PROBLEMS AND POTENTIAL

BY

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Summary

In a series of 39 fetuses, continuous intrapartum transcutaneous PO_2 recordings were made using a commercially available skin electrode, applied to the shaven fetal scalp. The weak correlation between transcutaneous measurements and umbilical blood PO_2 at delivery is believed to be due to scalp ischaemia produced by 'head to cervix' pressure during labour. This 'tonsure' effect presents a major obstacle to the use of surface electrodes for intrapartum blood gas monitoring from the fetal scalp in clinical obstetrics. Modification of the current technique may allow it to be used reliably for research.

IF the skin is heated sufficiently, oxygen in its dilated capillaries will diffuse readily to the surface, the increased PO_2 of blood caused by the raised temperature is offset by oxygen consumption in the intervening skin, and the PO_2 at the skin surface provides a faithful representation of general capillary PO_2. That general principle, first demonstrated by Baumberger and Goodfriend (1951), has been exploited during the last 10 years by Huch *et al* (1973 and 1977) in the development of a reliable non-invasive method of measuring PO_2 in the fetus and young infant. The developed sensor (Huch *et al*, 1973) is a Clark type oxygen polarographic electrode with three platinum microcathodes (diameter 15 μm) and a silver anode which can be heated to between 43 and 45°C in an electrolyte solution separated from the skin by a Teflon membrane 25 μm thick.

Commercial electrodes now available include the Draeger 'Transoxode', which closely resembles that developed by Huch *et al* (1973 and 1977), a macrocathode (diameter 4 mm) type developed by Roche-Kontron and a single microcathode (diameter 20 μm) by Radiometer. Comparative studies by Huch and Huch (1977) and Le Soeuf *et al* (1978), using the Draeger and Roche-Kontron electrodes on infants where the central PO_2 was known from simultaneous aortic samples, demonstrated the superiority of the Draeger system, due at least partly to its lower oxygen consumption.

In the fetus, where direct access to arterial blood samples is impossible, measurements of transcutaneous PO_2 ($tcPO_2$) on the scalp can, of necessity, only be compared to indirect measures of hypoxia of which the fetal heart rate pattern has been the most usual. Few attempts have been made to compare $tcPO_2$ either with direct estimates of PO_2 in scalp blood samples, or with PO_2 in umbilical cord blood.

The object of this study was to examine the relation of $tcPO_2$ measured on the presenting scalp with clinical and biochemical indices of fetal oxygenation at delivery.

MATERIALS AND METHODS

For the reasons given above, the Draeger Transoxode was chosen for the major series of transcutaneous recordings. The $tcPO_2$ and 'relative heat' (the electrical energy required to maintain a constant temperature of the heating element) were recorded on two channels of a 4 channel EM 740 recorder (Elcomatic, Glasgow).

The two other channels recorded fetal heart rate (measured either by an external ultrasonic probe or internal scalp electrode via a Sonicaid FM_2 monitor) and uterine contractions using an external tocometer.

The fetal Transoxode and accessories were sterilized by immersion for ten minutes in aqueous glutaraldehyde (Cidex, Livingston, Scotland).

The electrode was calibrated using oxygen-free nitrogen and ambient PO_2 (about 20 kPa depending on barometric pressure). The zero point was achieved by placing the electrode face down in a sterile well and delivering the calibration gas from a side vent below the level of the electrode. In practice, zero calibration once achieved was extremely stable. Calibration in air was necessary before each application, as repeated immersion in glutaraldehyde appears to accelerate oxidation of the silver anode, leading to an upward drift of the upper calibration point. Regular cleaning of the anode using jeweller's rouge is sufficient to restore the electrode's performance.

Application of the electrode requires adequate vizualization of the fetal scalp. In practice we found the minimum cervical dilatation required was 4 cm. An enlarged version of the conventional short 3 cm diameter amnioscope was developed by Rocket of London for this purpose.

In spite of a contrary Scandanavian view (Löfgren and Jacobson, 1977) we agree with Huch *et al* (1977) that accurate placement and recording require that the scalp be shaved before application of the electrode. Rocket of London have developed a single blade razor with a Luer male connection which can be fitted to the distal end of the familiar fetal blood sampling knife handle.

The applicator for placement of the electrode has also been modified from the Huch prototype to protect the lateral insertion of the cable and to prevent torsion of the electrode.

Adhesion of the electrode to the fetal scalp is of critical importance. Initially Histacryl Blue (Braun, West Germany) was chosen as a rapid water-activated acrylic adhesive, however, we have now found that Superfast 415 (Loctite, Ireland) which is a high viscosity cyanoacrylate adhesive gives stronger adhesion to the fetal scalp so that even rotational forceps deliveries can be performed without dislodgement of the electrode. Nevertheless, when required, the electrode can be quickly and easily removed by lifting its edge.

The heating element was set for a temperature of 44°C in accordance with recommendations by Huch *et al* (1977) and Le Soeuf *et al* (1978).

We have found that the entire procedure can be accomplished perfectly well with the patient in the left lateral decubitus position thus eliminating the need to place the patient in the potentially hazardous lithotomy position. The procedure, like amnioscopy itself, was perfectly feasible without anaesthesia, but for primigravidae epidural analgesia was an advantage.

Once applied, the electrode required a period of 10 to 15 minutes to equilibrate with tissue PO_2: this corroborates the findings of Huch *et al* (1977).

Fetal blood sampling for PO_2 measurement was also performed in the lateral decubitus position using the standard Saling and Schneider (1967) technique. The samples were immediately analysed, using an 1L 613 Micro pH/Blood Gas Analyser; samples of cord arterial blood obtained from doubly clamped segments of umbilical cord were similarly analysed. Quality control of the 1L 613 analyser was maintained using gas equilibrated aqueous buffer solutions (1L Blood Gas Control ampoules). Twice weekly analysis using these ampoules showed that the analyser remained accurate for PO_2 values of 7·6 kPa to within $\pm 0{\cdot}60$ kPa (recommended target value $= 7{\cdot}60 \pm 0{\cdot}67$ kPa).

Comparisons were made between the PO_2 measured on microblood samples obtained from the fetal scalp and simultaneous values recorded by the Transoxode. Comparisons were also made between the PO_2 obtained from cord arterial blood at delivery and the $tcPO_2$ value at the time of 'crowning' of the fetal head. In published comparisons it is usual to calculate the average $tcPO_2$ in the 5 or 10 minutes before delivery, but the PO_2 is frequently quite variable over that period; that at 'crowning' tends to be much more consistent.

PATIENTS AND RESULTS

Of 39 patients with a vertex presentation, 29 primigravidae and seven multiparae were studied for periods ranging from 30 minutes to 12 hours (mean 3·9 hours); in the remaining three, adhesion of the electrode was unsatisfactory. Twenty-six of the patients had lumbar epidural analgesia before application of the electrode at a cervical dilatation of 4 cm or more (mean 6·4 cm).

In 17 patients, the electrode remained in place until delivery, and in 11 of these, postnatal recordings were made up to a maximum of 25 minutes following delivery. Five out of the 11 perinatal recordings had intrapartum recordings in excess of three hours and these are depicted in Figure 1, which shows the general progressive decline in the $tcPO_2$ value, often to or near zero. Patient No. 3 shows a five hour intrapartum period where the $tcPO_2$ remained at zero with a rapid recovery following forceps delivery. This infant had Apgar scores of 1 at one minute and 9 at five minutes and the umbilical arterial blood pH was 7·292; PCO_2, 6·87 kPa; PO_2, 1·8 kPa; and base deficit was 0·7. Spontaneous respiration was established at four minutes and subsequent neonatal progress was uneventful. The other four patients shown in Figure 1 were all delivered of babies in good condition with Apgar scores of 8 or above. In each case the $tcPO_2$ on crowning of the fetal head was considerably below the PO_2 obtained from the umbilical artery at delivery. This phenomenon is better seen for the 17 patients presented in Figure 2 where the electrode remained firmly applied until the moment of delivery. In general, the $tcPO_2$ values were below 1 kPa with the corresponding cord arterial PO_2 values almost all in excess of 1·5 kPa. The weak correlation ($r = 0·35$) between intrapartum $tcPO_2$ values and simultaneous scalp blood PO_2 measurements is seen in Figure 3. For a $tcPO_2$ value of 0·5 kPa, for example, simultaneous scalp blood samples gave values of 2 kPa, 2·1 kPa and 2·7 kPa. The correlation between $tcPO_2$ and umbilical artery PO_2 was zero. The 'relative

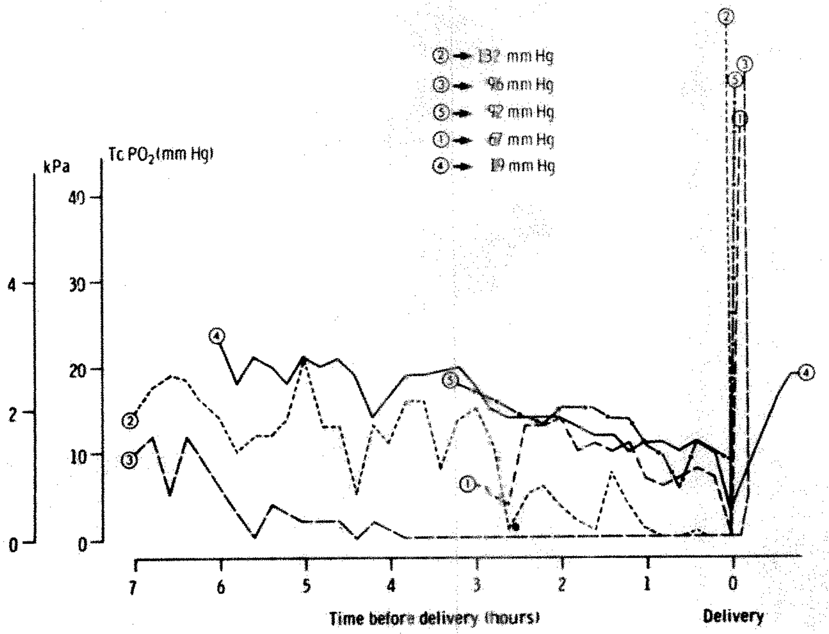

FIG. 1

Perinatal transcutaneous PO_2 continuous recordings five fetuses. Note the progressive fall towards delivery and the prolonged anoxia in patient No. 3. (→n mm Hg indicates stable postnatal value).

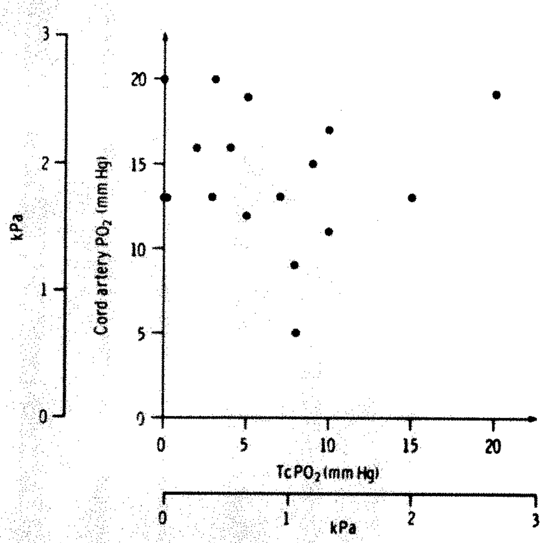

FIG. 2

Relation between transcutaneous scalp PO$_2$ at delivery and umbilical artery PO$_2$ (r = 0·35).

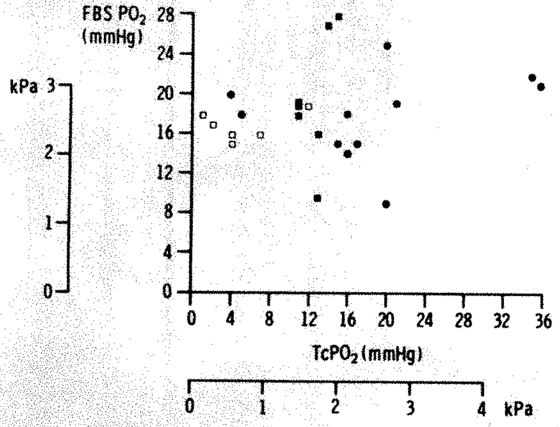

FIG. 3

Relation between intrapartum transcutaneous PO$_2$ values and simultaneous scalp blood PO$_2$ measurements (r = 0).
□ = Measurements in patient No. 1
■ = Measurements in patient No. 2
● = Single measurements in eleven other patients

heating' power is that required to maintain the temperature of the electrode at the pre-determined value—in this case 44°C. It is presumed that heating power will increase when increased blood flow underneath the electrode allows more effective removal of heat which tends to cool the electrode. For this reason the 'relative heat' reading was used by Huch *et al* (1977) not only to indicate that the electrode had come loose from the scalp but also as an index of skin perfusion.

Our recordings of 'relative heat' indicate that it is not a reliable indicator of scalp adhesion. During deliberate detachment of the electrode from the scalp postnatally—relative heating power was frequently seen to change little if at all until the electrode was completely separated and blood and mucus cleaned from the surface of the membrane. Furthermore, during conditions of presumptive scalp ischaemia in the second stage of labour, where tcPO$_2$ at delivery was found to have considerably underestimated systemic arterial PO$_2$ (as measured in cord artery), no clear pattern of decreasing 'relative heat' could be seen to indicate falls in scalp perfusion. Where recordings were continued during delivery of the fetus and beyond, a characteristic rise of 50 to 70 mW was found following delivery of the head but this returned to the predelivery values over a period of five minutes and then rose again once the electrode was removed from the neonatal scalp.

In common with Huch *et al* (1977), we found no more than a loose association between fetal heart rate abnormalities and falls in scalp tcPO$_2$. Where there was an entirely normal fetal heart rate or merely Type I decelerations, the tcPO$_2$ ranged from 0 to 3·9 kPa (0 to 29 mm Hg) and on average the lowest level recorded was 0·9 kPa (6·9 mm Hg). Where there were Type II decelerations the range of tcPO$_2$ during the time of the decelerations ranged from 0 to 3·7 kPa (0 to 28 mm Hg) and the lowest level recorded was, on average, 0·7 kPa (5 mm Hg). Moreover, in eight normal patients without any signs of fetal distress, terminal tcPO$_2$ values of less than 1·2 kPa were found.

When 4 l/minute of oxygen was given to the mother intranasally, fetal tcPO$_2$ could increase by as much as 1·3 kPa (10 mm Hg) over a period of five minutes, but this response was not consistent.

In three patients, epidural top-ups associated with hypotensive episodes produced significant falls in the tcPO$_2$ to values less than 1·2 kPa (9 mm Hg) and in one patient this recurred with every top-up given.

Attempts to record tcPO$_2$ from the presenting breech were made in six patients (not included in this series). These were singularly unsuccessful due to the irregularity and softness of the breech which prevented satisfactory application of the electrode.

Postnatal assessment of the 39 babies to whom the electrode was applied revealed only one minor blistering of the scalp following a five hour recording. This healed within a week and subsequent follow-up at six months revealed no impairment of hair growth at the site. The fetus having the longest intrapartum recording of 12 hours was also assessed at the end of the first week of life and again eight months after delivery. The initial erythema disappeared within a week and there was good hair growth. Residual cyanoacrylate adherent to the scalp disappeared during the period of hospitalization, presumably as skin desquamated.

One recording was associated with the development of maternal pyrexia and fetal tachycardia. An intrauterine infection with Group B haemolytic streptococci was diagnosed and treated successfully in mother and infant with penicillin. This application of five hours duration began 15 hours after rupture of membranes. The streptococci were isolated from the electrode following its removal from the scalp.

DISCUSSION

The poor relation between $tcPO_2$ values before delivery and cord arterial PO_2 is of much more concern than the poor relation between $tcPO_2$ and scalp blood PO_2. The latter may be at least in part due to aerobic contamination of 'arterialized' capillary blood samples, tending to produce higher PO_2 values.

Even the good correlation between scalp blood PO_2 and simultaneous $tcPO_2$ shown by Schneider *et al* (1979) demonstrates no more than that both methods measure what oxygen is available in the same area of scalp, which is not to say that either is a true reflection of the 'central' arterial PO_2. Our finding of a considerbale discrepancy between $tcPO_2$ and umbilical artery PO_2, which is almost always higher, suggest that scalp is often uniquely hypoxic presumably due to occlusive local ischaemia. We refer to this as the 'tonsure' effect.

When local capillary blood flow falls below 3 ml/100 g/minute in any site, then there is a rapid decline in the recorded $tcPO_2$. Pressures of between 2 and 10·6 kPa exerted by the electrode on the underlying skin of the adult forearm and neonatal chest have been shown to reduce $tcPO_2$ readings to zero, and in postnatal and adult scalp, the skin pressures required to reduce capillary blood flow and $tcPO_2$ to zero are of the order of only 1·2 to 6·6 kPa (O'Connor *et al*, 1979). The variation in pressures required may reflect variation in arterial and hence capillary blood pressure in different sites as well as variation in the elasticity of skin and underlying tissues.

Fall *et al* (1979) suggested that exposure of the scalp to air during vaginal examination resulted in falls in recorded $tcPO_2$. But Froese and Burton (1957) stated that scalp vasoconstriction was unlikely to occur in response to reduced temperatures and we have not observed the changes reported by Fall *et al* (1979). However, in adult scalp we have demonstrated that scalp vasoconstriction—(as measured by reduced clearance of radiosodium from a subcutaneous injection into the scalp) does occur in response to voluntary hyperventilation in air. On the other hand, scalp vasodilatation has been demonstrated by a raised sodium clearance and increased $tcPO_2$ during ingestion of hot liquids, such as coffee or tea. These findings suggest that the scalp circulation is extremely labile and may, under a variety of circumstances, give a falsely high or low indication of PO_2 when measured by means of a surface electrode. If it is assumed that the transcutaneous PO_2 electrode gives a reliable estimate when the skin circulation is unimpeded, then what is needed is a continuous recording of the pressure on the scalp recorded simultaneously with fetal scalp $tcPO_2$. This would at least allow identification of changes synchronous with variations in scalp compression which could be ignored. Falsely low $tcPO_2$ values could also occur in association with falls in fetal capillary scalp blood flow not associated with scalp compression but due to reflex vasoconstriction ('the diving reflex') occurring in conditions of relative oxygen deficiency (Dawes and Mott, 1959).

Factors such as scalp compression and peripheral skin vasoconstriction might operate in unison to reduce fetal scalp $tcPO_2$.

Our overall impression is that applications very early in labour, when the electrode lies above the zone of cervical compression, will give much more reliable indications of fetal oxygenation than when descent of the head places the electrode below the zone of maximum compression. Unfortunately, it is at present impossible to identify this end point.

Arterial blood supply to the scalp is by means of four main branches. The occipital, posterior auricular and superficial temporal arteries are branches of the external carotid and these supply the region between occiput and vertex. The supra-orbital arteries are terminal branches of the internal carotid and these might, if not equally compressed by the encircling cervix, tend to produce a tcPO$_2$ in the anterior scalp which more accurately reflected cerebral oxygenation.

One must conclude that fetal transcutaneous PO$_2$ monitoring in its present form is of little clinical value to the practising obstetrician. Furthermore the 'tonsure' effect may also have implications for the correct interpretation of fetal scalp blood pH measurements (O'Connor *et al*, 1979).

Nevertheless, applications of the electrode 10 to 15 minutes before delivery would allow sufficient equilibration time, so that investigation of birth asphyxia (at present hampered by the imprecision of the Apgar score or a single biochemical analysis of cord blood) could be put on a more objective basis.

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CONTINUOUS MEASUREMENT OF TRANSCUTANEOUS FETAL OXYGEN TENSION DURING LABOUR

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Summary

Transcutaneous scalp oxygen tension ($tcPO_2$) was measured during labour in 40 fetuses, using a modified Clark electrode (Radiometer, Copenhagen). In 24 of the fetuses the recordings were of good quality during the second stage of labour. After delivery the acid-base status and oxygenation of the umbilical cord blood was measured. A correlation was found between the $tcPO_2$ and umbilical artery oxygen saturation ($r = 0{\cdot}56$, $p<0{\cdot}01$) and umbilical artery PO_2 ($r = 0{\cdot}56$, $p<0{\cdot}01$). Furthermore, a positive correlation was found between the area beneath the recorded $tcPO_2$ curve during the last 10 minutes and the umbilical artery pH ($r = 0{\cdot}50$, $p<0{\cdot}05$). The data suggest that continuous transcutaneous PO_2 measurement may be of value in monitoring high risk patients during labour.

NEONATAL studies have shown that there is a close correlation between transcutaneous oxygen tension ($tcPO_2$) and the oxygen tension of the central arteries of the newborn (Huch *et al*, 1974).

Most of the investigations of fetal transcutaneous PO_2 measurements have concentrated on defining normal values during the first stage of labour. But for a comparison of $tcPO_2$ and the biochemical and physical state of the newborn infant, the most appropriate period is that immediately before delivery.

PATIENTS AND METHODS

Patients

We recorded the fetal $tcPO_2$ in forty consecutive patients (20 primiparae, 20 multiparae). In order to accumulate as much experience as possible in fetal $tcPO_2$ monitoring we monitored both normal and high-risk patients. As all patients in our department are already offered cardiotocogram (CTG) monitoring during labour, and as there have been no reports of complications using fetal $tcPO_2$ monitoring, we found it acceptable to monitor normal patients.

No women had narcotics in labour, but three had epidural analgesia, all being successfully monitored for fetal $tcPO_2$ until delivery. Three women were delivered by Caesarean section, only one of them because of suspected fetal distress. Eight women were delivered by outlet forceps or vacuum extraction, six of them because of suspected fetal distress.

The electrode (Radiometer, Copenhagen) consisted of two elements: a cathode measuring the oxygen tension, and an anode containing a heating element and a thermistor measuring the temperature of the electrode.

The heating element produces hyperaemia of the skin and the oxygen tension of the skin surface approximates the central arterial oxygen tension with increasing skin temperature, although they never become identical. In earlier papers (Eberhardt and Mindt, 1975; Haschke *et al*, 1976; Löfgren, 1978; Huch *et al*, 1977) a skin temperature between 43 and 45°C was selected, the highest temperature not being used on premature infants.

Raising the electrode temperature above 44°C does little to approximate the $tcPO_2$ to the central arterial PO_2 (Le Souëf *et al*, 1978), and as this temperature has never caused skin burns during obstetrical monitoring, we have selected an electrode temperature of 44°C in the present study.

The temperature of the electrode was kept constant by the thermistor of the heating element. The energy needed for heating the element (mW), the temperature of the electrode (°C), and the oxygen tension (mm Hg) were all displayed on a measuring unit (TCM 1, Radiometer, Copenhagen).

The electrode was first calibrated at an oxygen tension of 0 mm Hg with a borax buffer solution (pH 9·18) containing a surplus of sodium sulphite, as this solution creates an oxygen tension closer to zero than does a solution of N_2 (Heitmann *et al*, 1967; Laver and Seifer, 1965). Subsequently, only a calibration at atmospheric oxygen tension was needed as the relationship between the oxygen tension and the electrode output is linear.

After calibration, sterilization was performed by means of a 3 per cent solution of formaldehyde and glutaraldehyde for at least 20 minutes as this procedure did not alter the calibration values of the electrode (see below).

We have used two different techniques for fixation of the electrode on the head of the fetus.

Glue-fixation. After rupture of the membranes and if the cervix was at least 4 cm dilated, an amnioscope (33 mm) was introduced. The electrode and a fixation ring (Fig. 1) were then held by the application tool seen in Figure 2. In the small holes of the fixation ring drops of glue (Histoacryl ®) were placed a few seconds before application. The electrode and the ring were then pressed firmly against the unshaven head of the fetus for two minutes. Finally, the position of the electrode was checked by vaginal examination.

Suction-fixation. The electrode was mounted in the fixation ring seen in Figure 1. During a vaginal examination the electrode was held between two fingers and placed at the side of the fetal head, under the uterine cervix. Suction (−300 mm Hg) was then applied through the groove of the fixation ring (Fig. 1). If the electrode fell off or the placement of the electrode was preventing obstetrical operations, only a vaginal examination was required to change the position of the electrode.

Fetal $tcPO_2$ values were stable 10 to 20 minutes after fixation to the fetal scalp using either method.

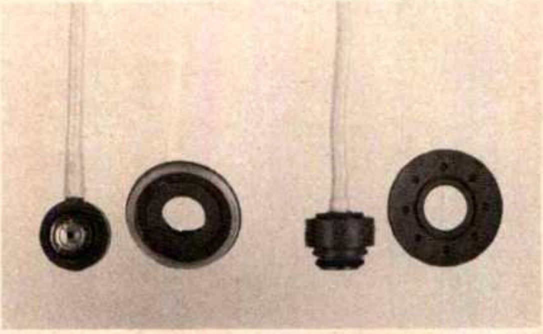

FIG. 1

Electrodes and application-rings for transcutaneous oxygen tension ($tcPO_2$) measurements. From left to right: (i) $tcPO_2$ electrode for suction-fixation, (ii) ring for suction-fixation, (iii) $tcPO_2$ electrode for glue-fixation, and (iv) ring for glue-fixation.

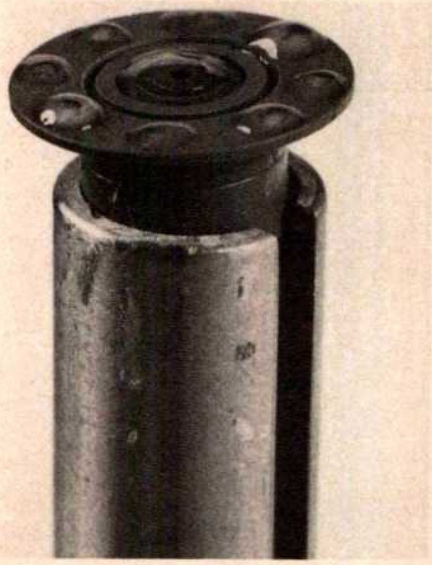

FIG. 2

Tool for application of the transcutaneous PO_2 electrode mounted in the application ring (glue-fixation).

All patients in the study were also monitored by a cardiotocograph using a spiral electrode and an intrauterine catheter or external detection of contractions. The fetal heart rate (FHR) and the contractions were recorded together with the $tcPO_2$ and the amount of energy needed to heat the electrode (HEAT) on a four-channel recorder (Linearcorder mark 3, Watanabe, Japan).

To get a picture of the fetal oxygen supply during the last part of labour, we measured the area beneath the recorded $tcPO_2$ curve by planimetry. We measured the area during the last 10 minutes (A10) and 30 minutes (A30) before delivery, the area beneath sudden rises due to vaginal examinations being subtracted.

The $tcPO_2$ values were not taken into account in the management of the delivery.

The electrode was considered correctly applied if the $tcPO_2$ readings were stable or if temporary changes occurred only in connexion with vaginal examinations. If the $tcPO_2$ values were unstable we considered the electrode to have been incorrectly applied and if labour was not too advanced a new application was tried. The recordings in which the electrode was considered correctly applied were classified as good, whereas other recordings were classified as unsuccessful.

At delivery, the umbilical cord was double clamped, if possible before the first gasp of the infant, and thereafter blood from the umbilical artery and vein was analyzed for pH, PCO_2, base-excess (BE), PO_2, and oxygen saturation (SAT) using autoanalyzers (ABL 2 and OSM 2, Radiometer, Copenhagen).

Finally we determined the drift of the electrode following sterilization in a 3 per cent solution of formaldehyde and glutaraldehyde for periods between 30 and 150 minutes.

RESULTS

When calibrated in atmospheric air, the drift of the electrode during sterilization was 0 to 7 mm Hg for periods ranging from 30 to 150 minutes, the mean drift being 2·9 mm Hg/hour (ten cases). As there was no drift from the zero calibration and as the electrode response was linear, the drift of the electrode in the range of fetal $tcPO_2$ (0 to 20 mm Hg) was very small.

Twenty-nine of the 40 recordings of $tcPO_2$ were of good quality but in five patients the electrode fell off or was removed before delivery (for reasons such as forceps delivery). Eleven recordings were unsuccessful. The distribution according to the fixation method is shown in Table I.

There was no correlation between the final $tcPO_2$ and the following: umbilical artery–BE, $-PCO_2$, and umbilical vein–BE, $-PCO_2$, –SAT, $-PO_2$. We found a positive correlation between the final $tcPO_2$ and umbilical artery PO_2 ($r = 0·56, p < 0·01$) (Fig. 3) and umbilical artery SAT ($r = 0·56, p < 0·01$).

A positive correlation was also found between A10 and umbilical artery pH ($r = 0·50, p < 0·05$). There was no correlation between A10, A30 and other umbilical artery and vein values.

The one-minute Apgar scores of 20 newborn infants were compared with the $tcPO_2$ of the last minute before delivery, the A10, and the A30. We found a significant ($p < 0·05$) difference between the 13 infants who had a high Apgar score (9 or 10) and the other seven infants (four

TABLE I

The quality of the $tcPO_2$ recordings (see text) according to the method of application

Fixation method	Quality of recording Good until delivery	Good until removed or fell off	Unsuccessful No.	Per cent
Glue (n = 21)	10	4	7	33
Suction (n = 19)	14	1	4	21
Total	24	5	11	28

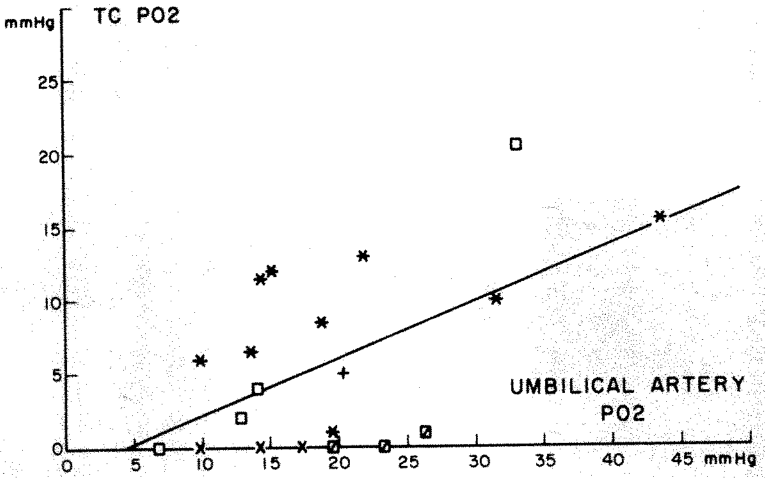

FIG. 3

Relation between $tcPO_2$ in the last minute before delivery and umbilical artery PO_2, grouped according to Apgar scores at one minute after delivery and to operative delivery for fetal distress.

□: Apgar score 0–8, no obstetrical operation for suspected fetal distress (CTG 'normal').

▨: Apgar score 0–8, outlet forceps/vacuum extraction for fetal distress.

★: Apgar 9–10, no obstetrical operations for fetal distress.

×: Apgar score 9–10, outlet forceps for suspected fetal distress.

The patient (□) with low Apgar score and high $tcPO_2$ (20 mm Hg) and high umbilical artery PO_2 (33 mm Hg) was delivered by Caesarean section for disproportion with a normal acid base state (pH 7·31) of the umbilical artery and with Apgar scores of 8 and 10 one and five minutes after delivery.

had a score of 8, two a score of 7 and one a score of 5). The infants with a high Apgar score had a mean last minute $tcPO_2$ of 6·7 mm Hg (SD 5·0 mm Hg, range 0 to 16 mm Hg) whereas the other infants showed $tcPO_2$ readings of 0, 0, 1, 2, 0, 4, and 3, respectively (mean 1·4 mm Hg). The infant delivered by Caesarean section (see Fig. 3) was omitted from these calculations.

DISCUSSION

We found a positive though weak correlation between the $tcPO_2$ during the last minute before delivery and the oxygen content of the umbilical artery blood (judged by PO_2 and SAT). The pH of blood coming from the fetus correlated with the recorded tissue oxygen tension during the last 10 minutes of labour.

A positive correlation between umbilical artery base excess and the $tcPO_2$ of the last 30 minutes of labour would be expected. The reason why we did not find a significant correlation could be because a long period of hypoxia is needed before a metabolic acidosis can develop, and we only had very few patients showing low $tcPO_2$ for longer periods. Although a decrease in the fetal oxygen supply should be expected to be accompanied by a decrease in the ability of the fetus to get rid of the CO_2, we did not find a positive correlation between the $tcPO_2$ during the last 30 minutes of labour and PCO_2 in the umbilical artery. The positive correlation between the umbilical artery pH and the oxygen tension during the last 10 minutes of labour (A10) might be explained by a cumulative effect of those two mechanisms, but more comprehensive series including hypoxic fetuses would be needed to show a possible positive correlation between the $tcPO_2$ and the PCO_2 and base excess.

The application of the electrode with glue gave 33 per cent unsuccessful recordings. This was due to the difficulty of distributing the glue evenly on the fixation ring. Also, the hair of the fetus could cause the electrode to fall off or measure incorrect values. Shaving of the fetal head might improve the results, but there are certain disadvantages in shaving: it might cause bleeding, it might influence the vascularization of the skin, and the parents might object.

The advantages of using suction-fixation of the electrode are that an amnioscope is not needed, the application can be made at a site of the fetal head outside the area seen through the cervical orifice, and it is easy to reapply the electrode if it falls off. Our first results seem to indicate that suction-fixation is superior to glue-fixation judged by the number of successful recordings (Table I). Since Löfgren (1978) found that the suction and glue application techniques made no difference to $tcPO_2$ levels in newborn infants or to the recording pattern, we feel justified in calculating our correlations using the combined results of both electrodes. This is corroborated in an unpublished study of six patients showing the same $tcPO_2$ level and changes using both a suction- and a glue-fixed electrodes simultaneously.

There is no published information about the relation between the area beneath the recorded $tcPO_2$ curve, or the $tcPO_2$ during the final minute of labour, and the status of the umbilical artery and vein blood.

Huch *et al* (1977) had 33 recordings of good quality from application which lasted until delivery among a total of 51 patients (65 per cent good recordings). We had 72 per cent good recordings. Huch *et al* (1977) also calculated the lowest $tcPO_2$ level during each recording. The distribution of these levels is in agreement with ours.

Although we found significant differences between the distribution of last minute $tcPO_2$, A10, and A30 in infants with high Apgar scores compared to those with an Apgar score of 8 or less at one minute, we had only one infant with an Apgar score of less than 7.

The value of $tcPO_2$ measurements on the fetal head, rests on the assumption that they are correlated with the PO_2 of the central arteries of the fetus. A recent paper (Jacobson and Löfgren, 1977) has shown a good correlation between $tcPO_2$ of the head and thorax of the newborn and the central arterial PO_2. There is also a close correlation between thoracic skin $tcPO_2$ and the $tcPO_2$ of the central arteries of the newborn (Huch *et al*, 1974).

Whether there is also a positive correlation between fetal $tcPO_2$ measured on the fetal head and the PO_2 of the central arteries of the fetus has not yet been investigated, but the correlation we found between fetal $tcPO_2$ and umbilical artery PO_2 at the time of delivery suggests that this may be the case. We believe that since the $tcPO_2$ is correlated with the central arterial PO_2 and pH, and since infants with Apgar scores of 8 or less tend to have a lower $tcPO_2$, it is a reasonable expectation that $tcPO_2$ will be related to fetal and neonatal health when more information has been accumulated.

ACKNOWLEDGEMENT

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AMNIOTIC FLUID PALMITIC ACID/STEARIC ACID RATIOS, LECITHIN/SPHINGOMYELIN RATIOS AND PALMITIC ACID CONCENTRATIONS IN THE ASSESSMENT OF FETAL LUNG MATURITY IN DIABETIC PREGNANCIES

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Summary

The lecithin/sphingomyelin (L/S) ratio, palmitic acid concentration and palmitic to stearic acid (P/S) ratio were estimated on samples of amniotic fluid obtained from 66 patients with diabetes. These were compared with similar estimates on amniotic fluid obtained from 127 non-diabetic patients. At 35 to 40 weeks, significant differences were observed between the L/S ratio and palmitic acid concentration in diabetics and non-diabetics, whereas the P/S ratio was similar in the two groups. The amniotic fluid L/S ratio, palmitic acid concentration, and P/S ratio were estimated on amniotic fluid obtained from 20 diabetic patients within 48 hours of induction, and the clinical outcome of the newborn infant was used to assess the predictive value of the three parameters. In 19 out of the 20 diabetics the P/S ratio correctly predicted fetal lung maturity, whereas the palmitic acid concentration was correct in 12 patients and the L/S ratio in only 10 patients.

THE lecithin/sphingomyelin (L/S) ratio and palmitic acid concentration determinations in amniotic fluid are used widely to predict fetal lung maturity. More recently palmitic acid concentration and stearic acid concentration in amniotic fluid expressed as the palmitic/stearic acid (P/S) ratio has been added as another index of fetal lung maturity (Alcindor *et al*, 1974; Schirar *et al*, 1975; O'Neil *et al*, 1978).

In the assessment of lung maturity in diabetes mellitus, both the L/S ratio and palmitic acid concentrations have proved unreliable (Donald *et al*, 1973; Dahlenburg *et al*, 1977; Hood *et al*, 1977; Mueller-Heubach *et al*, 1978).

This paper provides evidence that the measurement of P/S ratio in the acetone insoluble fraction is a more reliable indicator of fetal lung maturity than either the L/S ratio or palmitic acid concentration in those pregnancies complicated by maternal diabetes.

PATIENTS AND METHODS

Between December 1974 and November 1978 the L/S ratio, palmitic acid concentration and P/S ratio were measured in amniotic fluid obtained from 66 diabetic women; 20 patients gave birth to live infants within 48 hours of the last estimate and were used for clinical correlation. Six patients were gestational diabetics and 14 were insulin dependent diabetics. The control group consisted of 127 non-diabetic patients.

Amniotic fluid samples were obtained either by trans-abdominal amniocentesis, at amniotomy, or at Caesarean section. Assessment of gestational age was made by (i) clinical history and examination of the mother, (ii) X-ray examination of the fetus after 32 weeks, (iii) ultrasound measurements of fetal biparietal diameters, and (iv) clinical and neurological assessment of the infant at birth. Diagnosis of respiratory distress syndrome (RDS) was based on any two of the following criteria at the age of 4 hours: (i) grunting respirations, (ii) a respiratory rate of more than 60 per minute, and (iii) sternal or intercostal retraction. Classification of the severity of RDS was determined by clinical evaluation during the first 24 hours of life and according to therapeutic means necessary to maintain adequate neonatal oxygenation.

Reagents and equipment

All reagents used were analytical grade obtained from British Drug Houses, with the exception of boron-trifluoride in methanol (20 per cent w/v), diethylene glycol succinate, and chromosorb W 80–100 mesh, acid washed and treated with dimethyl dichloro silane (chromosorb WAWDMCS) which were obtained from Merck.

Identification of the fatty acids in the amniotic fluid was made by comparison with a series of standard curves constructed from pure fatty acid methyl esters obtained from Sigma.

The gas chromatograph used for the fatty acid analysis was a Pye Unicam series 104 equipped with a 2 m column, a flame ionisation detector and an autosolid injection block.

Preparation of the amniotic fluid

Amniotic fluid was centrifuged at 3000 revolutions/minute (2124 *g*) for 30 minutes at 4°C and the L/S ratio was measured immediately. If the palmitic acid concentration and P/S ratio were not measured at the same time, the specimen was frozen at −20°C and assayed within 72 hours.

Preparation of the acetone insoluble phospholipid and measurement of the L/S ratio

The amniotic fluid acetone insoluble phospholipid fraction was prepared by a modification of the method of Gluck *et al* (1967). The L/S ratio was estimated by thin layer chromatography on plastic backed silica gel strips and the lecithin and sphingomyelin spots were identified by staining with bromothymol blue as previously described (Andrews *et al*, 1976). For the assessment of palmitic acid concentration and the P/S ratio, the acetone insoluble extract was prepared in the same manner as for the L/S ratio.

Measurement of fatty acids and calculation of the palmitic acid concentration and P/S ratio

Free fatty acids were hydrolyzed and methylated by a modification of the method of Van Wijngaarden (1967). The acetone insoluble residue was hydrolyzed with 1·5 ml of 0·5 M sodium hydroxide in methanol under reflux on a heating block at 80°C for five minutes. Methylation was accomplished by the addition of 1·6 ml of boron trifluoride in methanol (20 per cent w/v) and refluxing for a further five minutes. A 50 μl volume of heptane was then added by microsyringe. Refluxing was continued for a further two minutes, then 2 ml of saturated aqueous sodium chloride were added and refluxing was continued for another three minutes, when the extraction of the methylated fatty acids into heptane was complete.

Five μl of the heptane extract containing the fatty acid methyl esters of the acetone insoluble extract were injected into the gas chromatograph. The liquid phase was 8 per cent diethylene glycol succinate on chromosorb WAWDMCS, with nitrogen as the carrier gas. The oven temperature was 180°C, the temperature for the injection block was set at 190°C, and for the flame ionisation detector 210°C.

The palmitic acid concentration was determined by comparing the peak areas of palmitic acid methyl ester to the peak area of the internal standard heptadecanoic acid methyl ester. The P/S ratio was determined by dividing the peak area of palmitic acid methyl ester by the peak area of stearic acid methyl ester.

The total recovery of the system with respect to palmitic acid was 87 per cent ± 3·6 per cent

(SD) on 25 estimations using an 8 mg/100 ml solution of α-β dipalmityl lecithin in chloroform.

RESULTS

Figures 1, 2, and 3 show the variation of the mean values (±1 SE) of the L/S ratio, palmitic acid concentration and P/S ratio with gestation for the diabetic and non-diabetic populations. The values observed for the L/S ratio and palmitic acid concentration were considerably higher in diabetic patients for the gestational period 35 to 40 weeks, whereas the P/S ratio for both populations was observed to be similar throughout gestation.

The calculated regression lines and the correlation coefficients (Figs. 1, 2, and 3) show a positive linear relationship in both populations for the three parameters for the gestational period 35 to 41 weeks. Probability values calculated by the t test (shown in Figs. 1, 2, and 3) indicate that during the gestational period 35 to 40 weeks there is a significant difference between the two populations in L/S ratio and palmitic acid concentration but no significant difference in the P/S ratio.

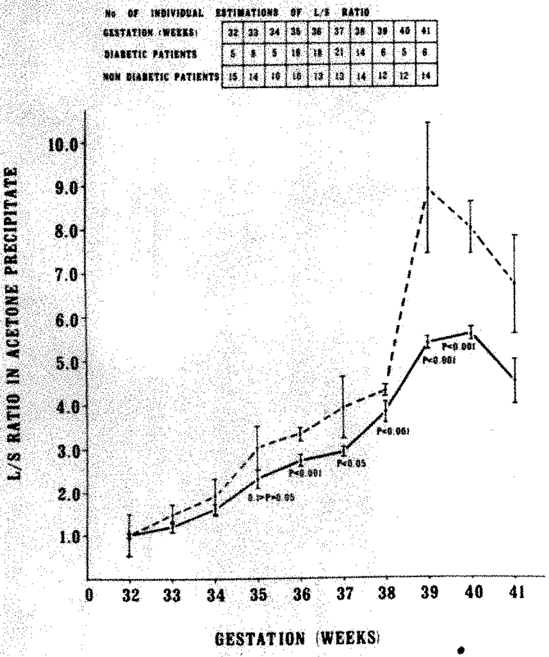

FIG. 1

L/S ratio versus gestation in diabetic pregnancies (- - -) compared with controls (—) showing the means and standard errors. Each point represents 5 to 21 patients for the diabetics and 10 to 15 patients for the controls. Linear regression and correlation coefficients were: $y = 0{\cdot}52x - 15{\cdot}92$, $r = 0{\cdot}94$ for the diabetics; $y = 0{\cdot}77x - 24{\cdot}01$, $r = 0{\cdot}88$ for the controls.

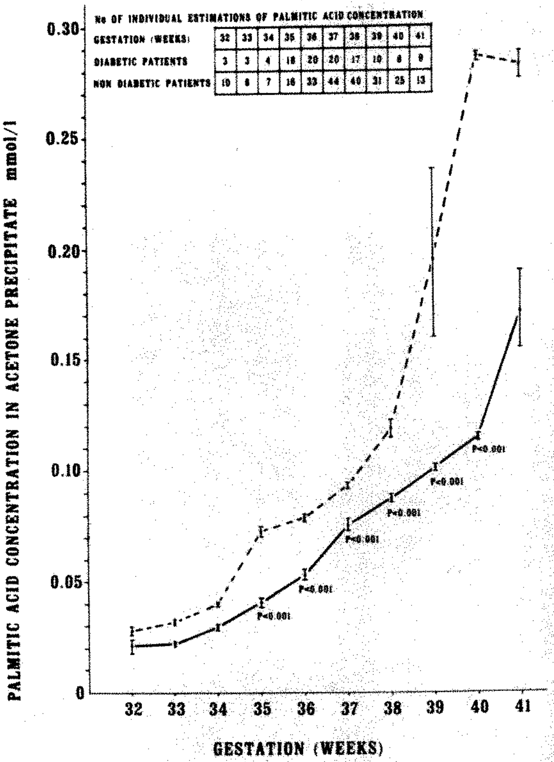

FIG. 2

Palmitic acid concentration versus gestation in diabetic pregnancies (- - -) compared with controls (—) showing the means and standard errors. Each point represents 3 to 20 patients for the diabetics and 8 to 44 patients for the controls. Linear regression and correlation coefficients were: $y = 30{\cdot}3x - 983{\cdot}4$, $r = 0{\cdot}93$ for the diabetics, $y = 15{\cdot}4x - 490{\cdot}9$, $r = 0{\cdot}96$ for the controls.

Table I shows in detail the values of L/S ratio, palmitic acid concentration, P/S ratio in amniotic fluid obtained within 48 hours of delivery, and the presence or absence of RDS in the newborn. The minimum criterion for lung maturity established at this hospital for L/S ratio is 2·0 (Andrews *et al*, 1976), palmitic concentration 0·042 mmol/l, and P/S ratio 4·5 (Andrews, 1978). These values are comparable to those observed by others (Warren *et al*, 1974; Alcindor *et al*, 1974; Schirar *et al*, 1975). Of the 20 infants, seven developed RDS (six mild, one severe) but all recovered.

No OF INDIVIDUAL ESTIMATIONS OF P/S RATIO

GESTATION (WEEKS)	32	33	34	35	36	37	38	39	40	41
DIABETIC PATIENTS	6	8	18	18	22	22	18	16	7	12
NON DIABETIC PATIENTS	11	9	13	26	32	40	40	31	26	15

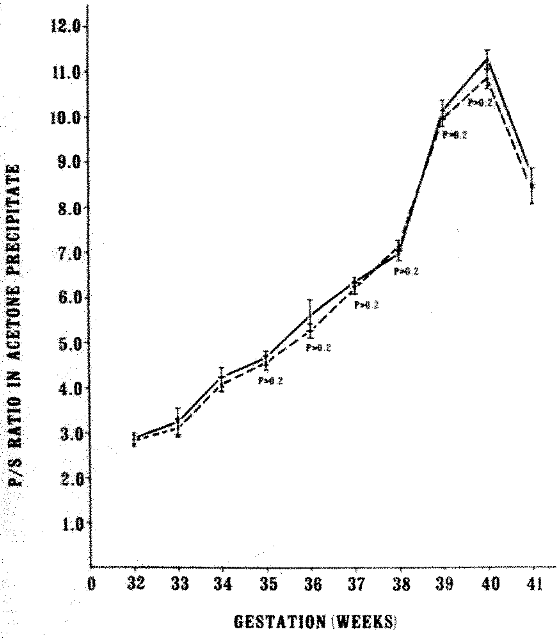

FIG. 3

P/S ratio versus gestation in diabetic pregnancies (- - -) compared with controls (—) showing the means and standard errors. Each point represents 6 to 22 patients for the diabetics and 9 to 40 patients for the controls. The linear regression and correlation coefficients were: y = 0·87x–25·34, r = 0·94 for the diabetics, y = 0·89x–25·92, r = 0·93 for the controls.

The P/S ratio correctly predicted fetal lung maturity in 19 out of the 20 patients (95 per cent). In the one patient in whom the P/S ratio failed to predict RDS (Table I, patient 20), the L/S ratio and palmitic acid concentration were also incorrect. The patient was a poorly-controlled insulin-dependent diabetic with unstable blood glucose throughout pregnancy. The palmitic acid concentration prediction was incorrect in eight patients (40 per cent). Four of the estimations gave a false positive value and four a false negative value. The L/S ratio prediction was incorrect in 10 patients (50 per cent). Four of the estimations gave a false positive result and six estimations gave a false negative result.

Serial estimations (Table II) were made on three patients to determine trends in the three parameters (No. 17, 13 and 3 in Table I). These showed an increase with gestational age except in patient No. 13 in whom palmitic acid concentration fell from a 'mature' to an 'immature' level and the infant developed RDS.

DISCUSSION

The unreliability of the L/S ratio in diabetic pregnancy is well established (Donald *et al*, 1973; Dahlenburg *et al*, 1977; Mueller-Heubach *et al*, 1978). Our findings confirm these reports, the mean values of the L/S ratio in the diabetic population being higher than those in controls at 35 to 40 weeks gestation.

In 10 of the 20 diabetics who gave birth 48 hours after the last estimation, the L/S ratio incorrectly predicted neonatal outcome. Four of these infants developed mild RDS but all recovered (Table I, patients No. 12, 13, 15 and 16). The amniotic fluid L/S ratio in all four babies with RDS had been well above the critical value of 2·0.

The measurement of palmitic acid concentration in the amniotic fluid as recommended by Warren *et al* (1974) does not appear to be any more reliable than the L/S ratio in predicting RDS in the diabetic. Hood *et al* (1977) observed fluctuations in palmitic acid concentration in serial estimations in 15 insulin-dependent diabetics and concluded that a single estimate of palmitic acid concentration was unreliable. In fact, four of their patients showed a decrease in palmitic acid concentration to a value equal to or lower than the critical palmitic acid concentration, and one developed RDS. This was confirmed by the incorrect prediction in 8 out of 20 patients we studied. In four patients, the palmitic acid concentration showed a 'mature' value well above the critical 0·042 mmol/l and yet the infants developed RDS. In patient No. 13 (Table II), a 'mature' value was observed at 34 weeks but an 'immature' value was obtained within 48 hours of birth and the infant developed mild RDS.

The differences between predictions based on L/S ratios and the occurrence of RDS in diabetic pregnancies apply also to palmitic acid concentrations. Comparison of Figure 2 with Figure 1 shows that the palmitic acid concentration for the diabetic population reflects the same trend as the L/S ratio. The mean values are much higher than in controls at 35 to 40 weeks gestation.

TABLE I

Information about 20 diabetic patients from whom amniotic fluid was obtained within 48 hours of delivery. The incidence of RDS in their infants can be compared with the predictions based on amniotic fluid L/S ratios, palmitic acid concentrations and P/S ratios

							Prediction		
Patient	Type of diabetes	Gestational age at delivery (weeks)	L/S ratio	Palmitic acid concentration (mmol/l)	P/S ratio	Infant status	L/S ratio	Palmitic acid concentration	P/S ratio
1	Insulin	36	1·3	0·028	3·7	Severe RDS	Correct	Correct	Correct
2	,,	36	3·0	0·082	4·6	Normal	,,	,,	,,
3	,,	35	3·1	0·087	5·2	,,	,,	,,	,,
4	,,	36	3·1	0·070	5·5	,,	,,	,,	,,
5	,,	36	5·9	0·069	6·4	,,	,,	,,	,,
6	Gestational	36	2·9	0·042	7·4	,,	,,	,,	,,
7	,,	37	2·4	0·045	5·2	,,	,,	,,	,,
8	,,	37	7·2	0·045	7·3	,,	,,	,,	,,
9	,,	36	1·7	0·078	3·5	Mild RDS	,,	Incorrect	,,
10	Insulin	35	1·4	0·058	3·6	,,	,,	,,	,,
11	,,	37	1·5	0·044	5·1	Normal	Incorrect	Correct	,,
12	Gestational	37	2·5	0·018	4·1	Mild RDS	,,	,,	,,
13	Insulin	35	2·6	0·038	3·7	,,	,,	,,	,,
14	,,	36	1·4	0·090	5·9	Normal	,,	,,	,,
15	,,	34	3·1	0·075	4·3	Mild RDS	,,	Incorrect	,,
16	,,	35	6·0	0·060	4·1	,,	,,	,,	,,
17	,,	33	1·7	0·027	4·5	Normal	,,	,,	,,
18	,,	31	0·6	0·021	4·6	,,	,,	,,	,,
19	Gestational	37	1·8	0·038	4·6	,,	,,	,,	,,
20	Insulin	36	1·6	0·033	4·3	,,	,,	,,	Incorrect

TABLE II

Serial estimates on amniotic fluid obtained from three diabetic patients to show trends in the L/S ratios, palmitic acid concentrations and P/S ratios

	Gestation (weeks)	L/S ratio	Palmitic acid concentration (mmol/l)	P/S ratio	RDS
Patient 17					
1st estimate	31	1·0	0·012	3·1	No
2nd estimate	33	1·7	0·027	4·5	
Patient 13					
1st estimate	34	1·7	0·050	3·3	Yes
2nd estimate	35	2·6	0·038	3·7	
Patient 3					
1st estimate	34	3·0	0·068	4·5	No
2nd estimate	36	3·1	0·087	5·2	

The predictive value of the amniotic fluid P/S ratio in diabetic and non-diabetic pregnancies was assessed by O'Neil *et al* (1978). Their results suggested a better correlation than those observed for palmitic acid concentration and L/S ratio, however, it should be noted that the time interval between the last estimate and birth was 72 hours and that the cold acetone precipitate was not used. In our series the P/S ratio predicted lung maturity correctly in 19 out of 20 patients (95 per cent) including the seven in whom the infants developed RDS.

Our results show that if the P/S ratio is determined within 48 hours of birth and the acetone precipitation of Gluck *et al* (1967) is used the accuracy of the assessment is improved. This is because in diabetics the stearic acid keeps pace with the fluctuation in palmitic acid concentration which is reflected in the constancy of the P/S ratio from around 32 weeks onwards. We conclude that the amniotic fluid P/S ratio should be used in preference to the L/S ratio and palmitic acid concentration for the prediction of fetal lung maturity in the presence of maternal diabetes.

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MODE OF DELIVERY AND THE LECITHIN/SPHINGOMYELIN RATIO

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Summary

Babies born by elective Caesarean section are more likely to develop the respiratory distress syndrome than babies born vaginally. We studied the amniotic fluid and pharyngeal lecithin/sphingomyelin (L/S) ratios in three groups of babies born at term: 20 were delivered vaginally after elective induction of labour; 20 were delivered by elective Caesarean section; and 14 by Caesarean section after spontaneous onset of labour. Babies born after induction of labour had higher pharyngeal L/S ratios than babies born by elective Caesarean section. Those born by Caesarean section after spontaneous onset of labour had significantly higher pharyngeal L/S ratios than those in both of the elective delivery groups. There were no significant differences in the amniotic fluid L/S ratios of the two groups who underwent elective delivery. Regression analysis showed a significant relationship between length of labour and increase in the L/S ratio. These results indicate that, during labour, there is a release of fetal lung surfactant into the airways.

BABIES most at risk of developing the respiratory distress syndrome (RDS) are those born before 37 weeks gestation, but clinical studies have revealed other factors, apart from prematurity, that may predispose to the development of RDS (DeSa, 1969). One of these is Caesarean section, as shown in the 1958 British Perinatal Mortality survey (Butler and Bonham, 1963; Butler and Alberman, 1969; Fedrick and Butler, 1970 and 1972) and other studies (Latham *et al*, 1955; Snyder, 1961; Usher *et al*, 1971; Cohen *et al*, 1960; Jones *et al*, 1975).

There is a higher incidence of death due to hyaline membrane disease in babies born by elective Caesarean section (47 per 1000 live births) than in babies born by Caesarean section after labour has commenced (3 per 1000) or by the vaginal route (2 per 1000) (Fedrick and Butler, 1970). This higher incidence associated with elective Caesarean section remains after correcting for differences in gestational age (Butler and Alberman, 1969).

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RDS is caused by a deficiency in the production of pulmonary surfactant (Avery and Mead, 1959). The amniotic fluid lecithin/sphingomyelin (L/S) ratio (Gluck *et al*, 1971) has been shown to be a reliable indicator of adequate fetal lung surfactant production and is now widely used before elective delivery.

The L/S ratio has also been measured in pharyngeal aspirates from newborn babies (Parkinson *et al*, 1978) and shows a close relation with the incidence of RDS. We found that pharyngeal L/S ratios are a little higher than amniotic fluid L/S ratios and suggest that a value of 2·5 is most likely to be equivalent to an amniotic fluid L/S ratio of 2 (10 per cent of babies with pharyngeal L/S ratios between 2 and 2·5 had RDS).

In this study the L/S ratio has been used to compare the surfactant status of three groups of babies: those born at term vaginally after elective induction of labour, those born by elective Caesarean section and those born by Caesarean section after labour had commenced.

PATIENTS AND METHODS

Patients

The first part of the study was on two groups of multiparous women who underwent elective delivery at 38 weeks gestation or later. Twenty women had labour induced by artificial rupture of the membranes and intravenous oxytocin infusion (Group A). Indications for induction of labour were: mild obstetric or social complications or both (9 patients), pre-eclamptic toxaemia (3 patients), raised blood pressure alone (3 patients), postmaturity (2 patients), small-for-dates fetus (2 patients) and previous neonatal death (one patient). Fourteen of the babies were delivered by normal vertex delivery, five had forceps deliveries and one was delivered by ventouse.

Twenty women had an elective Caesarean section (Group B); none of them was in labour at the time of operation and the indications were a previous Caesarean section (9 patients), cephalopelvic disproportion (7 patients) or both (3 patients) and placenta praevia (1 patient).

In addition, a third group (Group C) of 14 babies were delivered by Caesarean section after their mothers had been in labour for at least four hours (range 4 to 30 hours). Indications for the Caesarean section were: failure to progress in labour (7 patients), fetal distress (3 patients), previous neonatal death (2 patients), cephalopelvic disproportion (one patient), previous Caesarean section (one patient).

Amniotic fluid specimens. In Group A, amniotic fluid was collected through an intrauterine catheter, inserted at the time of artificial rupture of the membranes for induction of labour. A further amniotic fluid specimen was obtained during the second stage of labour in 16 women. In Group B, amniotic fluid was obtained by needle aspiration at the time of the Caesarean section prior to the incision in the lower segment of the uterus. No amniotic fluid was collected in Group C. No sample contaminated with blood or meconium was included in the study.

Pharyngeal aspirates. All 54 babies had their airways cleared at birth using a mucus extractor. The extractors were retained and the fluid collected in the trap was analysed for the L/S ratio.

Method of analysis. Amniotic fluid L/S ratios were determined by the planimetric method of Gluck *et al* (1974). The pharyngeal aspirates were diluted with saline before being analysed by the same method.

Respiratory distress syndrome. All babies were observed after birth for RDS using the criteria described by Dewhurst *et al* (1973). One baby from each of groups A and B developed mild RDS.

Birth asphyxia. Since birth asphyxia can also predispose to RDS and lower L/S ratios have been found in this condition (Parkinson *et al*, 1978), only babies who were not asphyxiated at birth (one minute Apgar score of 6 or more) were included in the study.

RESULTS

The results were compared using nonparametric statistics (the Mann Whitney U test) which are more appropriate for this analysis than a comparison of means. There was no significant difference between the amniotic fluid L/S ratios of the two groups who had an elective delivery (Groups A and B), which indicates that they were comparable before obstetric intervention (Table I).

Table I also gives the mean L/S ratios of the pharyngeal aspirates from the babies in all three

TABLE I

Mean amniotic fluid and pharyngeal L/S ratios in the three groups

Group	L/S ratios Mean ± SD Amniotic fluid	 Pharyngeal aspirate
A. Induction of labour, vaginal delivery	(1st) 2·55 ± 0·83 (2nd) 2·32 ± 0·64	3·12 ± 0·99
B. Elective Caesarean section	2·71 ± 0·87	2·55 ± 0·83
C. Caesarean section in labour	—	3·61 ± 0·91

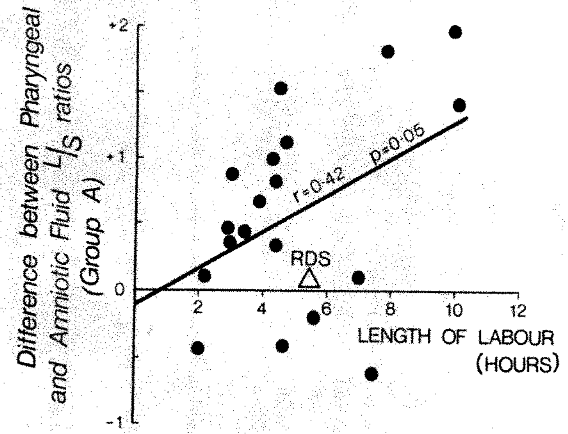

FIG. 1

Difference between the babies' pharyngeal L/S ratios and their pre-labour amniotic fluid L/S ratios, related to length of labour.

groups. Babies in Group A, those born after induction of labour, had significantly higher L/S ratios than babies born by elective Caesarean section ($p<0{\cdot}05>0{\cdot}025$). Babies in Group C, those born by Caesarean section after labour had commenced, had significantly higher L/S ratios than babies in both the other two groups ($p<0{\cdot}001$), even after excluding from the analysis the two babies who had RDS.

In Group A, the total length of labour was related to the difference between their pharyngeal and amniotic fluid L/S ratios. Figure 1 shows the results, which gave a significant correlation between length of labour and increase in the L/S ratio ($p = 0{\cdot}05$). It can be seen from Figure 1 that four babies had a lower pharyngeal L/S ratio than that of their amniotic fluid; one of them was born after a short labour (two hours) and another had labour induced because a previous baby died neonatally from intrapartum anoxia. The mean age of the mothers of these four babies was 33·75 ± 2·9 years, compared with 27·0 ± 3·4 years in the rest of the group ($p<0{\cdot}001$).

There were no significant differences between the L/S ratios of the first and second amniotic fluid specimens in Group A.

The two babies who developed RDS had pharyngeal L/S ratios of 2·38 (Group A) and 1·36 (Group B). Amniotic fluid L/S ratios were 2·34 and 1·12 respectively. The baby born after induction of labour had little increase in its L/S ratio from the first amniotic fluid value and was delivered by forceps because of a prolonged second stage of labour.

Table II shows the percentage of non-RDS babies in each group who had pharyngeal L/S ratios below 2·5. A higher proportion of the results of babies born by elective Caesarean section fell into this category (53 per cent).

DISCUSSION

Our results indicate that some factor occurring in labour may be stimulating the release of lung surfactant from the Type II alveolar cells into the alveoli. Since there is a flow of lung fluid up the trachea, this newly released surfactant also appears in the fluid aspirated at birth from the pharynx. It is known from animal studies (Gluck *et al*, 1970) that, once spontaneous respiration begins, there is an enormous increase in surfactant release into the airways. Our study suggests that this release of surfactant is actually stimulated by labour in the hours before birth, as both groups of babies whose mothers were in

TABLE II

Percentage of babies in each group with pharyngeal L/S ratios below 2·5

Group	Total No. of babies	L/S ratios below 2·5 (per cent)
A	19	32
B	19	53
C	14	14

labour before delivery had higher L/S ratios than the babies born by elective Caesarean section. It is possible that in the four patients in Group A, where an increase in the L/S ratio failed to occur, labour did not have its usual stimulatory effect. Walters and Olver (1978) have produced evidence to show that lung liquid absorption begins in early labour and may be initiated by catecholamines. It is possible that absorption of lung liquid and release of surfactant from its reservoir in the Type II cells, may be synergistic actions to facilitate the onset of normal breathing at birth.

Brice and Walker (1977) measured crying vital capacity in babies born vaginally and by Caesarean section and found that crying vital capacity was lower in the Caesarean section group and did not reach the values of the other group until the third day of life. These babies were also more likely to suffer from transient tachypnoea of the newborn. It has been suggested (Kelnar and Harvey, 1977; Hallman *et al*, 1977) that transient tachypnoea is a very mild form of RDS, caused by minimal surfactant deficiency.

Our study confirms previous biochemical studies in which only amniotic fluid was investigated (Cabero *et al*, 1976; Craven *et al*, 1976; Whittle *et al*, 1977). These have all suggested that there is a release of surfactant during labour which seems greater in spontaneous than induced labour (Whittle *et al*, 1977). Our study also supports the clinical evidence of the incidence of RDS in these three groups of babies.

We wish to emphasise that our findings are for babies born at term. Stewart *et al* (1978) have shown that low birth weight babies (weighing less than 1·5 kg) have a greater chance of survival if born by Caesarean section.

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EPIDURAL ANALGESIA AND PLACENTAL BLOOD FLOW DURING LABOUR IN PREGNANCIES COMPLICATED BY HYPERTENSION

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Summary

Placental blood flow was measured during the first stage of labour in pregnancies complicated by essential hypertension or severe pre-eclampsia using a ^{133}Xe clearance technique before and after segmental epidural analgesia. Analgesia was produced with 0·5 per cent plain bupivacaine in six patients with essential hypertension and in 11 patients with severe pre-eclampsia. After segmental epidural analgesia the placental blood flow was slightly but insignificantly improved in most of the patients with pre-eclampsia and in half of the patients with essential hypertension, thus suggesting this analgesic method to be safe in hypertensive pregnancies in the absence of any substantial change in systemic blood pressure.

AN ideal obstetric analgesic method should not hamper the placental blood flow, and segmental epidural analgesia during the first stage of labour was found not to affect the intervillous blood flow in normal pregnancies (Jouppila *et al*, 1978*b*), when measured by a new quantitative ^{133}Xe-method (Rekonen *et al*, 1976).

There is evidence that in pregnancies complicated by essential hypertension or pre-eclampsia, placental blood flow can be seriously reduced (Browne and Veall, 1953; Käär *et al*, 1979), and the fetus may have low oxygen reserves (Bonica, 1972*b*). Any further decrease in intervillous blood flow would seriously affect fetal well-being. Epidural analgesia has been recommended by many authors as the analgesic method of choice in toxaemic labours (Moir, 1976; Janisch *et al*, 1978). The sympathetic blockade achieved by epidural analgesia has been observed to cause vasodilatation in the lower body (Bonica, 1972*a*), and Janisch *et al* (1978) have shown that epidural analgesia significantly improves the placental blood flow in late toxaemic pregnancies.

The aim of the present study was to examine the effect of segmental epidural analgesia on intervillous blood flow during labour in pregnancies complicated by essential hypertension or pre-eclampsia.

METHODS

The patients studied were six women with essential hypertension and 11 women with severe pre-eclampsia (Table I). These hypertensive diseases were classified according to the recommendations of the American Committee of Maternal Welfare (Dieckmann, 1952). All the labours of the pre-eclampsia group were induced

TABLE I

Gestational age, birth weight and Apgar scores of the newborn, also the individual values for maternal blood pressure and intervillous blood flow before and after analgesia.

Patient group	Gestational age (weeks)	Birth weight (g)	Apgar score		Blood pressure (mm Hg)		Intervillous blood flow (ml/minute/100 ml)	
			1 minute	5 minutes	Before epidural	After epidural	Before epidural	After epidural
Essential hypertension								
1	38	3260	9	9	150/110	120/90	214	276
2	38	4350	8	8	130/90	130/90	229	217
3	38	3600	9	10	150/90	150/90	305	195
4	37	3700	1	2	150/80	150/80	264	294
5	38	4100	8	9	140/80	140/80	230	195
6	40	4320	9	9	150/80	140/90	166	248
Mean	38·0	3888	7·3	7·8	148/88	138/87	235	238
± SD	± 1·3	± 438	±3·1	±2·9	± 8/11	± 12/5	± 43	± 38
Pre-eclampsia								
7	37	2970	9	9	155/110	140/100	64	131
8	37	3930	7	8	110/80	110/80	128	96
9	39	3850	8	9	140/80	140/80	219	358
10	38	2900	10	10	140/90	140/90	86	86
11	37	2950	9	9	150/90	120/70	282	231
12	37	3260	9	9	120/80	120/80	255	275
13	38	3080	10	9	140/90	140/90	179	188
14	37	2800	9	9	170/110	170/110	116	128
15	38	3700	9	9	150/80	140/90	75	86
16	38	3620	9	6	120/70	130/80	125	149
17	38	3160	9	10	170/105	180/100	119	300
Mean	37·6	3293	8·9	8·8	143/90	139/88	150	184
± SD	± 0·7	± 409	±0·8	±1·1	± 21/14	± 23/13	± 74	± 94

by amniotomy or oxytocin infusion or both. Three of the hypertensive labours started spontaneously, but oxytocin was also used in these patients to accelerate the labour. Thus all the patients were receiving an infusion of oxytocin during the flow measurements. The placenta was located by ultrasound B-scanning and the placental site was marked on the maternal abdominal wall. Only the patients whose placenta was located on the anterior wall of the uterus were included in the study. Informed consent was obtained from each patient.

Segmental epidural analgesia with the distribution between T_{10} and T_{12} was provided for pain relief during the first stage of labour when cervical dilatation was 2 to 5 cm (mean 3·4 cm). The analgesic agent used was 4 ml of 0·5 per cent bupivacaine (20 mg). The mothers received 500 ml of Ringer-lactate as an intravenous infusion and were lying in a 15° left lateral tilt position when the epidural injection was made; they remained in the same position for at least 30 minutes afterwards. Subsequently a more lateral position was allowed. Maternal arterial pressure was measured every three minutes for the first 30 minutes after the epidural injection. Fetal heart rate and uterine activity were monitored continuously. The analgesic effect was good or excellent in all the patients. In the pre-eclampsia group there were two deliveries by vacuum extraction. In the essential hypertension group one Caesarean section had to be performed because of cephalopelvic disproportion discovered during the late first stage. This baby had Apgar scores of 1 and 2 at one and five minutes, but was resuscitated and recovered well. All the other infants had Apgar scores of 7 or more.

Placental blood flow was measured immediately before the epidural injection and 15 to 20 minutes after the onset of analgesia by the ^{133}Xe method described in detail by Rekonen *et al* (1976).

The measurements were compared statistically using paired t test and Student's t test.

RESULTS

The mean initial intervillous blood flow (IVBF) was significantly lower in the pre-eclampsia group than in the essential hypertension group ($p < 0 \cdot 05$). After the epidural analgesia the IVBF values did not differ significantly from each other in the different groups (Table I).

In the essential hypertension group, IVBF improved in 3 of the 6 patients and decreased in the other 3 (Table I). The mean IVBF values before and after analgesia did not differ significantly.

In the pre-eclampsia group IVBF improved in 9 of the 11 patients (Table I) but the mean IVBF values before and after analgesia did not differ significantly from each other.

Following analgesia a fall in maternal blood pressure of 10 per cent or more from the initial systolic value occurred in two patients: one in the pre-eclampsia group, the other in the hypertension group. In the pre-eclamptic patient the flow decreased from 282 ml/minute/100 ml to 231 ml/minute/100 ml, whereas in the hypertension the flow increased from 214 ml/minute/100 ml to 276 ml/minute/100 ml. No pathological fetal heart rate (FHR) changes could be detected as a consequence of the analgesia. In two patients (No. 3 and 15), however, a loss of baseline variability could be detected during both the flow measurements. The IVBF values were low in patient No. 15. In patient No. 3 the flow value before analgesia was at the same level as the mean values of the series; after analgesia a significant fall of IVBF was observed in this patient. The birth weight of 3 of the infants of these 17 mothers (patients No. 7, 10 and 14) were below the 10th centile (Bäckström and Kauppinen, 1969). The initial IVBF values in these patients were below average and only patient No. 7 showed a substantial increase of IVBF after the block (Table I).

DISCUSSION

In pregnancies complicated by essential hypertension and pre-eclampsia, vasoconstriction may be a major influence in the decrease of uterine and placental blood flow (Bronatek *et al*, 1973; Janisch *et al*, 1978). Thus vasodilatation in the lower body caused by epidural blockade could benefit placental perfusion, provided that the perfusion pressure was maintained (Janisch *et al*, 1978). The present study showed that in patients with pre-eclampsia the initial mean IVBF was significantly lower than in patients with hypertension. This difference, however, disappeared as a consequence of epidural analgesia, which shows that in pre-eclampsia, especially, epidural analgesia has a favourable effect on the placental blood flow. This might be due to the fact that in pre-eclampsia the vascular changes are acute and transient, and react more rapidly to sympathetic blockade than in essential hypertension where the vascular changes are already chronic.

In one patient (No. 3) with essential hypertension a 30 per cent fall in IVBF could be seen without any change in blood perssure. The error of the Xenon method is ±20–30 ml/minute/100 ml (Jouppila *et al*, 1978*a*). This cannot explain this relatively large decrease (110 ml/minute/100 ml). The birth weight of this infant was 3600 g and Apgar scores 9 and 10 at one and five minutes, supporting the view of Greiss (1973) that a fetus tolerates well a short term decrease of IVBF. This patient also demonstrated a loss of baseline variability in FHR during both flow measurements. The other patient with a similar FHR pattern was in the pre-eclampsia group and the IVBF values were already very low before analgesia (patient No. 15); this patient showed no change of blood pressure during analgesia. Apart from these two patients no other pathological FHR patterns were related to epidural analgesia. It has been shown before that pathological FHR changes are few as a consequence of segmental epidural analgesia and if they exist they are mostly related to maternal hypotension (Jouppila *et al*, 1977; Collins *et al*, 1978).

In the present study we could not detect any greater blood pressure changes as a consequence of the analgesia. In two patients (No. 1 and 11) a slight fall in pressure could be seen, and in patient No. 11 with pre-eclampsia, a slight simultaneous decrease in IVBF could be observed. This agrees with the findings of Bronatek *et al* (1973), who reported that uterine blood flow was dependent on maternal blood pressure especially in pre-eclamptic patients.

The present findings concerning the toxaemic patients in labour differ from the findings of Janisch *et al* (1978). They found a significant increase of placental blood flow in pre-eclamptic pregnancies in connection with epidural analgesia. The improvement of placental blood flow in our patients was not significant or so marked as in their patients. The difference in the results could, however, be explained firstly by the difference in the doses of the analgesic agent and thus the extent of the sympathetic blockade. The amount of bupivacaine in our study was 4 ml of a 0·5 per cent solution instead of 10 to 18 ml of a 0·25–0·35 per cent solution administered by Janisch *et al* (1978). Our study was also performed during active labour, whereas Janisch *et al* (1978) measured the placental blood flow changes in the last few weeks of pregnancy without any uterine contractions. This fact may modify the results. If we compare our flow values with the values obtained between 35 and 40 weeks gestation before labour by Käär *et al* (1979), who used the same method of flow measurement, it appears that our values are greater. Our flow measurements were performed between successive uterine contractions in the beginning of the first stage of labour, when the intervals between the contractions were 3 to 4 minutes. In the curve of isotope decay the first 2 to 3 minutes represent the IVBF, so the IVBF measurement can be well done between the contractions if the interval between them is over 3 minutes. During a contraction, IVBF is known to be reduced (Greiss and Gobble, 1967). Thus the explanation for the difference in IVBF observed in these different series may lie in compensatory improvement of the flow through the intervillous space between the contractions in order to meet fetal requirements. Our flow measurements were done just after the cessation of a uterine contraction and thus at the time of the compensatory improvement of IVBF. Hence, the placental blood flow measurements during the last weeks of pregnancy and those during active labour cannot be directly compared with each other. Our assumption is also supported by the fact that our flow values were at the same high level as the values in our previous study of the effect of segmental epidural analgesia on placental blood flow during labour in normal pregnancies (Jouppila *et al*, 1978*b*).

Our findings suggest that low dose bupivacaine segmental epidural analgesia can be recommended as a method of choice for obstetric analgesia in hypertensive and pre-eclamptic patients provided that the maternal blood pressure does not fall significantly. The changes in IVBF were insignificant but a tendency for their increase in pre-eclamptic patients was reassuring.

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CIRCULATING LEVELS OF PREGNANCY SPECIFIC β_1 GLYCOPROTEIN IN LATE PREGNANCY: NYCTOHEMERAL AND DAY-TO-DAY VARIATION, AND VARIATION DURING LABOUR

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Summary

Circulating levels of pregnancy-specific β_1 glycoprotein have been determined in a number of physiological situations in late pregnancy. The apparent variation in five subjects studied over a 24-hour period was not in excess of that due to the assay. Excess variation was apparent in 2 of 11 subjects studied daily for up to 8 days, and in 6 of 16 patients studied serially during labour.

Pregnancy-specific β_1 glycoprotein (Schwangerschaftsprotein 1 or SP_1) (synonyms for SP_1 are PSβG, Towler *et al*, 1976; PAPP-C, Lin *et al*, 1974) is one of a new generation of recently identified proteins produced by the human placenta (Klopper and Chard, 1979). Clinical studies on SP_1 measurement in late pregnancy have shown that it may be a useful index of fetal wellbeing (Chard and Grudzinskas, 1979). However, there is little information on the time-to-time variability (Towler *et al*, 1976) and variation during labour of SP_1 levels in maternal blood in late pregnancy. The present study was designed to investigate the variation of circulating SP_1 levels over a 24-hour period, day-to-day variation for up to 8 days, and fluctuations during labour.

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MATERIALS AND METHODS

A total of 150 samples was collected from five ambulant volunteers (gestation 36 to 39 weeks) who were subsequently delivered of a live normal infant. In all patients venous blood was obtained at 15-minute intervals for two hours and hourly for a further 22 hours. Seventy-five samples were collected from 11 ambulant outpatients (gestation 36 to 39 weeks) who had normal pregnancies. Venous blood was obtained daily for up to eight days. A further 174 samples were obtained from 16 patients undergoing induction of labour. The first sample was obtained immediately before induction; further samples were obtained at hourly intervals, and more frequently during the second and third stages of

TABLE I

Nyctohemeral variations of maternal serum SP_1 levels in five patients examined over a 24-hour period. Thirty samples were available from each patient. Within-assay variation was established by 20 repeat determinations on one sample from each patient

	Patient samples			Control samples				
Patient	Mean SP_1 (mg/l)	C of V (per cent)	Variance (H)	Mean SP_1 (mg/l)	C of V (per cent)	Variance (C)	F value (H/C)	Probability (P)
1	423	6·8	841	476	6·9	1089	0·77	>0·05
2	349	7·4	676	476	6·9	1089	0·62	>0·05
3	176	11·9	441	170	9·4	256	1·72	>0·05
4	202	9·4	361	170	9·4	256	1·41	>0·05
5	454	8·4	1444	502	7·4	1369	1·05	>0·05

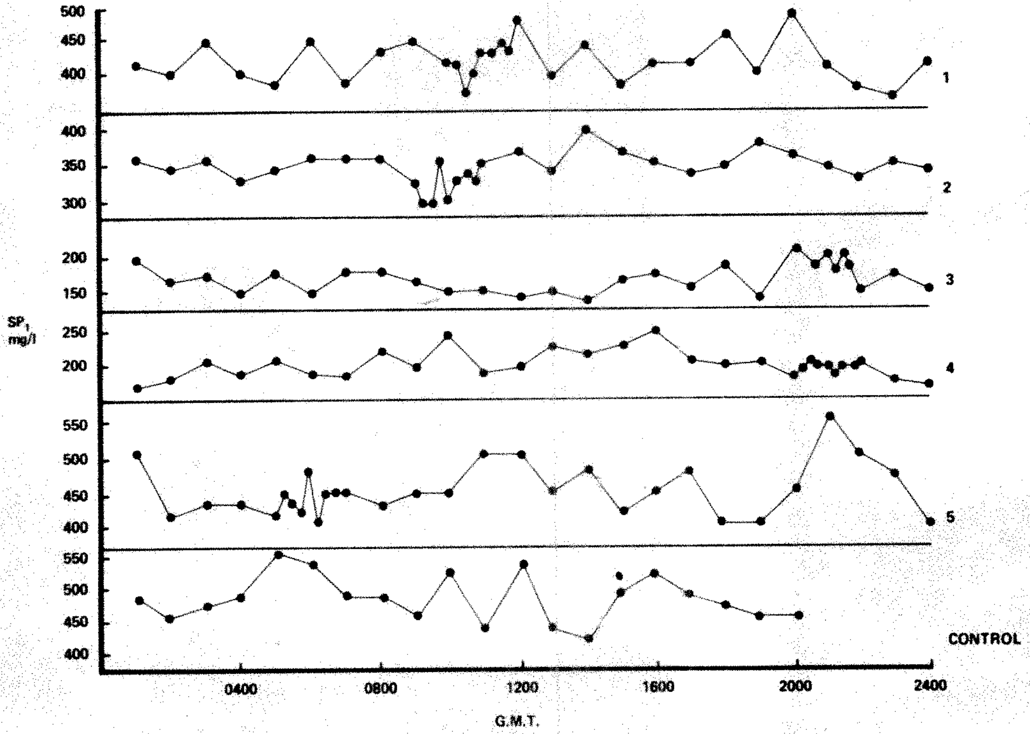

FIG. 1

Serum SP_1 levels in five patients over a 24-hour period.

labour. Induction of labour was performed by artificial rupture of the membranes followed by intravenous infusion of oxytocin. Serum was separated within two hours of collection and stored at −20°C until assay. Measurements of SP_1 were performed by radioimmunoassay (RIA) as described previously (Gordon *et al*, 1977). Each assay included 20 repeated determinations on the first sample to establish within assay variation. Sample variances were calculated for each subject and compared with assay variance by the 'F' test.

RESULTS

In all five subjects studied over a 24-hour period, the variation of SP_1 was not in excess of that which could be attributed to the assay (Table I, Fig. 1).

In 2 of the 11 subjects studied daily for up to 8 days the variation of SP_1 was in excess of that which could be attributed to the assay (Table II, Fig. 2); there was no obvious pattern to the variation.

In 6 of the 16 patients studied during labour, the fluctuations of circulating SP_1 levels were in excess of that which could be attributed to the

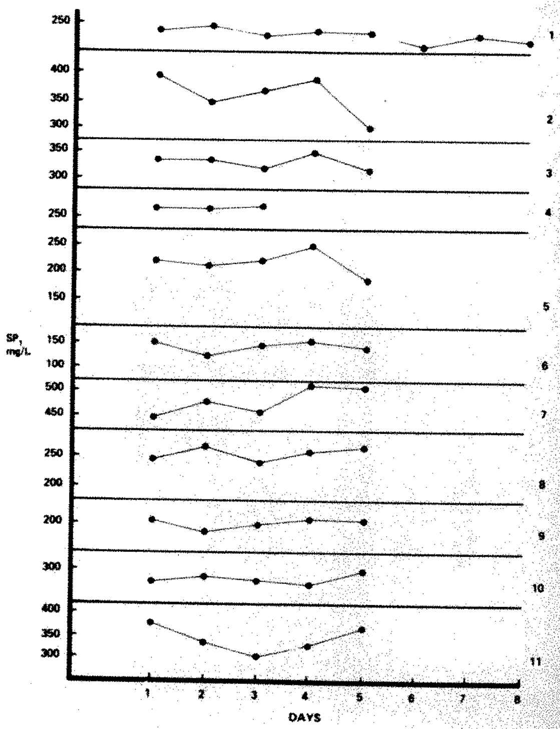

FIG. 2

Serum SP_1 levels in 11 patients sampled daily for up to 8 days.

TABLE II

Day-to-day variation of maternal serum SP_1 levels in 11 patients studied over a 5-day period. The number of samples available from each patient is shown in the second column. Within-assay variation was established by 20 repeat determinations on one sample from each patient

	Patient samples				Control samples				
Patient	No. of samples	Mean SP_1 (mg/l)	C of V (per cent)	Variance (H)	Mean SP_1 (mg/l)	C of V (per cent)	Variance (C)	F value (H/C)	Probability (P)
1	8	222	5·9	169	151	3·7	31·4	5·39	<0·05
2	5	371	11·6	1849	365	6·3	529	3·49	>0·05
3	5	342	3·7	156·2	365	6·3	529	0·29	>0·05
4	3	266	1·3	12·2	365	6·3	529	0·02	>0·05
5	5	215	10·6	529	151	3·7	31·4	16·87	<0·01
6	5	140	6·6	86·5	151	3·7	31·4	2·76	>0·05
7	5	483	5·5	718·2	461	7·4	1156	0·62	>0·05
8	5	257	5·3	182·2	365	6·3	529	0·34	>0·05
9	5	201	4·6	84·6	151	3·7	31·4	2·70	>0·05
10	5	128	6·1	60·8	151	3·7	31·4	1·94	>0·05
11	5	341	6·3	1108·9	365	6·3	529	2·10	>0·05

TABLE III

Intrapartum variation of maternal serum SP_1 levels in 16 patients. The number of samples available from each patient is shown in the second column. Within assay-variation was established by 20 repeat determinations on one sample from each patient

	Patient samples				Control samples				
Patient	No. of samples	Mean SP_1 (mg/l)	C of V (per cent)	Variance (H)	Mean SP_1 (mg/l)	C of V (per cent)	Variance (C)	F value (H/C)	Probability (P)
1	6	366	6·4	552	476	6·9	1089	0·50	>0·05
2	17	253	10·1	650	170	9·4	256	2·53	<0·05
3	11	319	14·7	2190	170	9·4	256	8·55	<0·01
4	7	252	13·5	1156	170	9·4	256	4·51	<0·05
5	14	157·5	9·9	243	170	9·4	256	0·94	>0·05
6	13	265	16·5	1918	170	9·4	256	7·49	<0·01
7	8	94·5	8·9	72	170	9·4	256	0·28	>0·05
8	15	151	9·9	222	170	9·4	256	0·86	>0·05
9	6	344	11·4	1544	170	9·4	256	6·03	<0·05
10	6	285	7·6	488	170	9·4	256	1·90	>0·05
11	12	339	11·5	1584	476	6·9	1089	1·45	>0·05
12	15	210	10·4	475	170	9·4	256	1·85	>0·05
13	18	152	11·2	289	170	9·4	256	1·12	>0·05
14	13	257	11·2	635	170	9·4	256	2·48	>0·05
15	16	271	9·5	660	170	9·4	256	2·57	<0·05
16	8	176	13·4	552	170	9·4	256	2·15	>0·05

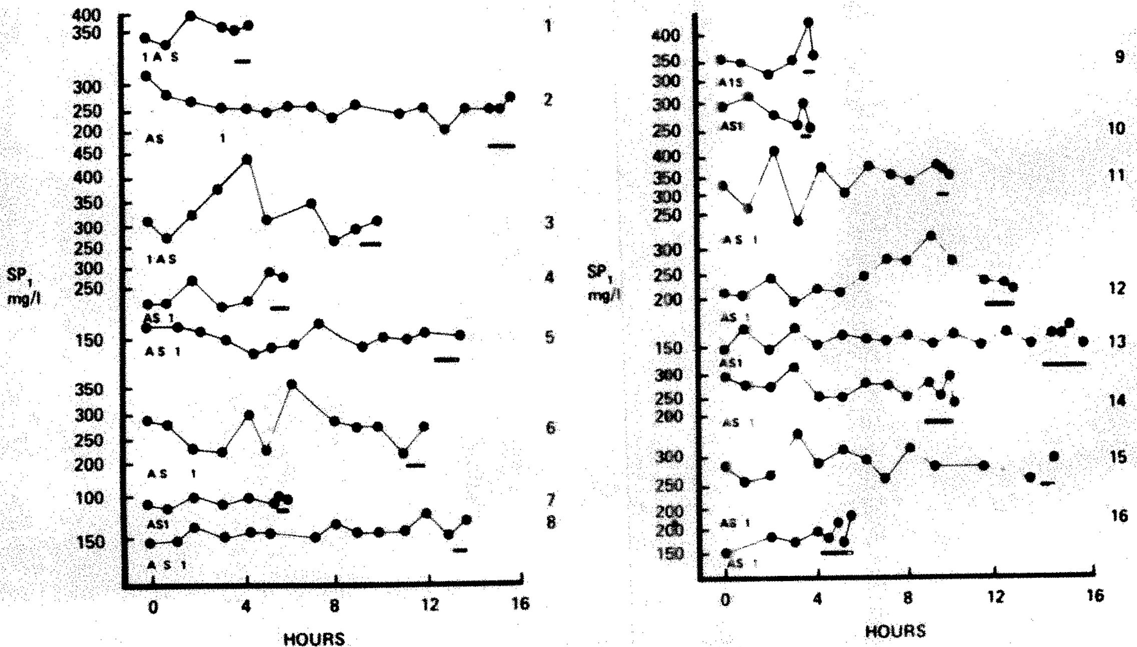

FIG. 3

Serum SP_1 levels in 11 patients sampled during labour (A = ARM; S = oxytocin infusion; 1 = onset of contractions; ■ = second stage of labour; □ = third stage of labour.

assay. In four subjects the variations were greater than those seen in any individual during late pregnancy (Table III, Fig. 3).

DISCUSSION

The present study describes for the first time SP_1 levels in individual patients over a 24-hour period. In all patients the variation of SP_1 levels was not in excess of that due to the assay itself, and no pattern was observed. In 2 of 11 patients who were sampled daily, the variation of SP_1 levels was in excess of those due to the assay itself, confirming the findings of Towler *et al* (1976) who used an immunodiffusion technique.

During induced labour, circulating SP_1 showed a greater variation in some subjects than in late pregnancy. This may well be due to mechanical emptying of the uteroplacental circulating during uterine contractions, though other studies (Klopper and Chard, 1979; Grudzinskas *et al*, 1979) have shown that the levels of SP_1 in retroplacental blood are the same as or lower than that in the peripheral blood.

The findings have the implication that a single sample from an individual will not necessarily be representative of all samples taken from the individual and hence the diagnostic significance of SP_1 determinations will be increased if serial samples are available. Furthermore, similar observations previously made on human placental lactogen (Pavlou *et al*, 1972), and plasma oestrogens (Klopper *et al*, 1975) in late pregnancy suggest that random nyctohemeral fluctuation may be characteristic of all trophoblastic products.

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CIRCULATING LEVELS OF PREGNANCY SPECIFIC β_1 GLYCOPROTEIN IN PREGNANCIES COMPLICATED BY DIABETES MELLITUS

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Summary

Circulating levels of SP_1 were measured in 20 insulin dependent diabetic women during the third trimester of pregnancy. With one exception, SP_1 levels were between the 80 per cent confidence limits of the normal range. The exception was a patient who was delivered of a normal infant at 37 weeks but had consistently low levels of SP_1 from 32 weeks until delivery, suggesting a specific defect in SP_1 synthesis.

PREGNANCY specific β_1 glycoprotein (SP_1) is one of a new generation of proteins recently isolated from late pregnancy blood (Tatarinov and Masyukevich, 1970) and placenta (Bohn, 1971). The clinical application of SP_1 measurement in the maternal circulation as an index of fetal wellbeing has been reviewed (Chard and Grudzinskas, 1979; Horne and Towler, 1979). The biological function of SP_1 during pregnancy is unknown although minor fluctuations in circulating levels of SP_1 after induced hypo- and hyperglycaemia (Tatra *et al*, 1976) have suggested a role in carbohydrate metabolism. Information on circulating levels of SP_1 in pregnancies complicated by diabetes mellitus is sparse (Tatra *et al*, 1974; Singh *et al*, 1979) and we now describe maternal blood levels of SP_1 during the third trimester in 20 insulin dependent diabetic women.

METHODS

A total of 72 blood samples was obtained from 20 insulin-dependent diabetic women from 31 to 40 weeks gestation. The mean duration of diabetes was 8·9 years (range 0·2 to 25 years); daily insulin dosage from 32 weeks onwards ranged from 24 to 168 units, and the mean preprandial blood sugar level from 32 to 36 weeks gestation ranged from 3·0 to 7·0 mmol/l. Control of the disease was considered to be satisfactory in all patients. Additional antenatal

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complications occurred in four patients (antepartum haemorrhage—2 patients; mild pre-eclampsia—2 patients). Eight patients were delivered by Caesarean section and 12 patients were delivered by the vaginal route, the average period of gestation being 37 weeks (range 34 to 40 weeks). All patients were delivered of a normal infant in good condition and no perinatal deaths occurred. The average birth weight was 3·318 kg (range 2·54 to 4·40 kg), and only two babies had a birth weight greater than the 95th centile of the normal range (Thomson *et al*, 1968).

Plasma was separated within one hour of collection and stored at −20°C. SP_1 determination was performed as described previously (Gordon *et al*, 1977).

RESULTS

Circulating SP_1 levels obtained from 31 weeks gestation onwards are shown in Figure 1. With the exception of four measurements, all SP_1 levels from diabetic subjects were distributed uniformly between the 80 per cent confidence limits of the normal range. The low SP_1 levels (32 weeks—5·0 mg/l, 33 weeks—4·3 mg/l, 34 weeks—3·5 mg/l, 36 weeks—4·8 mg/l) were collected serially from one patient who was delivered at 37 weeks gestation of an infant, weighing 3·34 kg, in good condition. Levels of SP_1 were unrelated to the blood glucose, daily insulin dosage and to the duration of the disease. Levels of SP_1 in the two patients with large babies did not differ from those in the group as a whole.

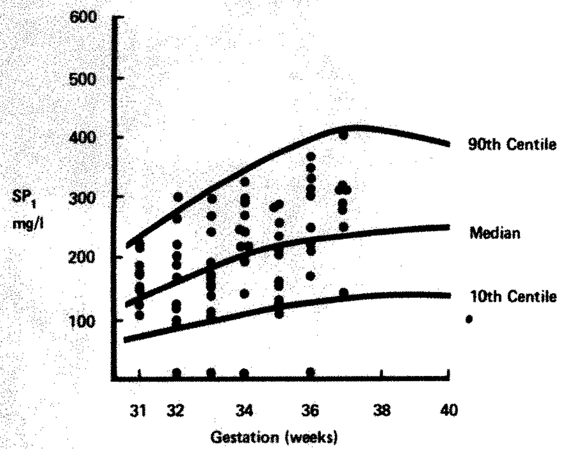

FIG. 1

Circulating levels of SP_1 in 20 women with insulin dependent diabetes.

DISCUSSION

This is the largest study at the present time of circulating SP_1 levels in insulin-dependent diabetic women. An earlier report (Tatra *et al*, 1974) described normal levels in two patients. Furthermore, Singh *et al* (1979) have described high levels of SP_1 occurring in patients with asymptomatic glucose intolerance in the third trimester. Maternal blood levels in all but one patient studied here were widely distributed between the 80 per cent confidence limits of the normal range. Furthermore, there was no apparent relationship between birth weight and SP_1 levels as the maternal levels in two women with macrosomic babies were above and below the median level for the normal range.

Studies on another specific placental protein, placental lactogen (hPL), in diabetic pregnant women have shown that the range of maternal levels is generally higher than that in a normal population, unless the pregnancy is complicated by placental malfunction when levels are reduced (Ursell *et al*, 1973). A similar pattern might have been expected with SP_1. That no such pattern was seen could perhaps be attributed to three factors. First, the populations studied were different. Second, the molecular heterogeneity of SP_1 recently described (Teisner *et al*, 1978) may reduce the precision of the assay, and the different forms of this molecule may vary in their biological activity. Third, control of diabetics in pregnancy has now achieved such a high level of sophistication that complications, whether clinical or biochemical, are virtually eliminated. In other words, it may be impossible at the present time to test the 'true' value of a biochemical parameter because the underlying condition is totally controlled.

It was of great interest that the circulating levels of SP_1 in one patient were the lowest levels recorded in any clinical study. Since this patient delivered a normal infant (birth weight 3·34 kg—placental weight 750 g), it can only be suggested that she had a rare and specific defect in SP_1 synthesis, and it is of interest that a similar deficiency has been reported with other placental products (such as placental sulphatase—France and Liggins, 1969). Whatever the cause, this must cast some doubt on the hypothesis of a vital function for SP_1 during pregnancy. Placental lactogen levels in this patient were all within the normal range (namely greater than the 10th centile).

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RELATION BETWEEN THE KARYOPYKNOTIC INDEX AND PLASMA OESTROGEN CONCENTRATIONS AFTER THE MENOPAUSE

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Summary

The karyopyknotic index correlated significantly ($p<0\cdot001$) with the plasma oestradiol but not plasma oestrone concentration in 38 postmenopausal women. This ties in with previous findings that postmenopausal women with superficial dyspareunia have a more severe degree of vaginal atrophy than asymptomatic women, and that oestradiol is probably more important biologically than oestrone.

THE karyopyknotic index (KPI) is the percentage of superficial squamous cells with pyknotic nuclei, excluding parabasal squamous cells (Wachtel, 1969), in a count of at least 200 cells. It is a popular method for determining cytologically the degree of oestrogenic proliferation of vaginal epithelium, although other factors such as prolapse, progestogens, and infection may also affect the KPI.

In a previous study (Hutton *et al*, 1978*a*) we found that postmenopausal women who complained of superficial dyspareunia had significantly lower mean plasma concentrations of oestradiol, but not of oestrone, than asymptomatic women of the same age, and concluded that low concentrations of oestradiol may be related to the severity of lower genital tract atrophy. The aim of this study was to determine the relationship between the plasma oestrogen concentrations and the KPI, in a further group of women with primary ovarian failure.

PATIENTS AND METHODS

Forty-four women who consented to uterine cavity aspiration (as described in another study, Hutton *et al*, 1978*b*) and who had had no oestrogen or progestogen therapy in the previous three months were included in this study. The women all had serum gonadotrophin concentrations which were in the menopausal range (Jacobs and Murray, 1976). Their mean age was $56\cdot0\pm8\cdot8$ (SD) years (range 46 to 80 years) and the mean interval since their last period was $7\cdot4\pm9\cdot2$ (SD) years (range 0·2 to 30 years).

A lateral vaginal wall smear was prepared at the time of uterine cavity aspiration, fixed in 95 per cent alcohol and stained by the method of Papanicolaou and Traut (1943). The KPI was determined from a minimum total count of 500 cells. In all smears in which superficial cells were seen, the relative number of parabasal cells was also determined since the presence of superficial squamous cells may result from mechanical irritation such as that caused by prolapse, rather than as a result of oestrogen stimulation. Women whose smears showed this pattern were excluded from the statistical analysis.

Plasma oestrone and oestradiol concentrations were determined in duplicate by radioimmunoassay (Hutton *et al*, 1978*a*) in blood samples that were taken immediately after the pelvic examination.

Since the KPI values were not of normal distribution, the correlation of each woman's plasma oestrogen concentration and KPI was determined by Spearman's rank correlation test.

RESULTS

The KPI was determined in 41 women, the lateral vaginal wall smear being too scanty for a reliable assessment in three women (two of whom had procidentia). The results from three other women were excluded from the analysis because they had second or third degree prolapse.

KPI values in these three other women with prolapse were 7 per cent, 14 per cent and 35 per cent and their respective plasma concentrations were 147 pmol/l, 147 pmol/l and 117 pmol/l for oestradiol and 290 pmol/l, 250 pmol/l and 220 pmol/l for oestrone.

The KPI and the plasma oestradiol and oestrone concentrations in the 38 women included in the statistical analysis are shown in Figures 1 and 2 respectively. A highly significant correlation ($r = 0{\cdot}581$; $p<0{\cdot}001$) was found between the KPI and the plasma oestradiol concentration but there was no significant correlation between the KPI and the plasma oestrone concentrations ($r = 0{\cdot}194$).

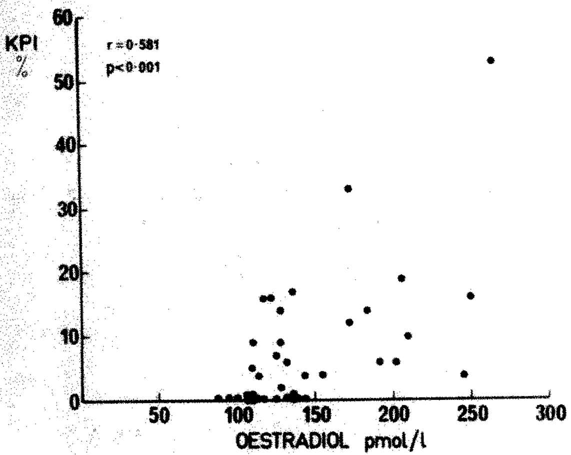

FIG. 1

The correlation between the karyopyknotic index and plasma oestradiol concentration in 38 postmenopausal women.

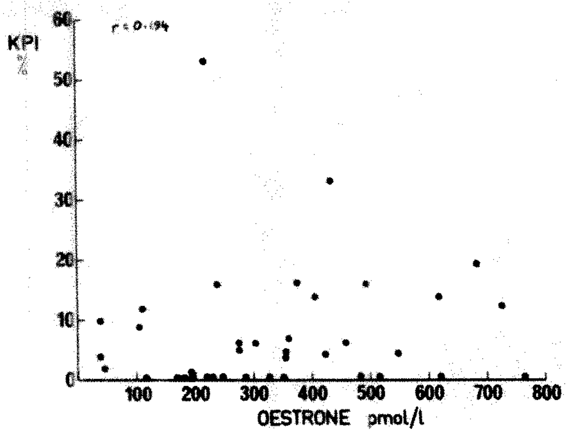

FIG. 2

The correlation between the karyopyknotic index and plasma oestrone concentration in 38 postmenopausal women.

DISCUSSION

The results of this study show that the degree of proliferation of the vaginal epithelium in postmenopausal women is correlated with the plasma concentration of oestradiol, whereas no such relationship exists for oestrone. This finding supports the conclusion (Hutton *et al*, 1978*a*) that postmenopausal women with superficial dyspareunia have a more severe degree of atrophy than asymptomatic women. The results are also in agreement with the view that oestradiol is the biologically important oestrogen.

This concept is consistent with the greater affinity of intracellular oestrogen receptors for oestradiol than for oestrone (Taylor, 1976). It remains to be determined if oestrone, which is present in the plasma of postmenopausal females, has any physiological significance or importance other than as a precursor for oestradiol.

The oestradiol and oestrone in the few women in this study in whom the plasma levels were greater than 180 pmol/l and 440 pmol/l, respectively, were probably derived largely from ovarian follicles that had not become depleted despite clinical and biochemical evidence suggestive of ovarian failure.

The results of this study supplement the finding by Schneider *et al* (1977) of a positive correlation of the KPI and the plasma oestradiol concentration in a group of premenopausal and postmenopausal women. However, in contrast to the present study, the plasma oestradiol levels in the postmenopausal women studied by Schneider were unmeasurable as the sensitivity of their oestradiol radioimmunoassay was 147 pmol/l.

Fluctuations in the plasma oestrogen concentrations throughout the day may have caused the wide scatter of the plasma oestradiol levels about the regression line in the present study and further studies are necessary to determine the accuracy with which the KPI reflects the plasma oestrogen status of postmenopausal women. Nevertheless, the results of this study suggest that this relatively simple cytological method may be a valuable aid in the management of postmenopausal women, particularly those requiring oestrogen therapy.

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PRIMARY CARCINOMA OF THE FALLOPIAN TUBE ASSOCIATED WITH TUBERCULOUS SALPINGITIS
A CASE REPORT

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Summary

A patient with co-existent carcinoma and tuberculosis of the Fallopian tube is described. Tuberculosis was diagnosed by the finding of numerous typical granulomata throughout the uterus, tubes and ovaries, and by exclusion of other possible causes of these; and carcinoma by the finding of solid tumour, with a marked anisocytic appearance, invading submucosa. Despite the well recognised epithelial hyperplasia seen in tuberculous salpingitis, there remains no evidence that the occurrence of carcinoma in such cases is other than fortuitous.

ABOUT 20 patients with co-existing carcinoma and tuberculosis of the Fallopian tube have been reported (Dickson *et al*, 1952; Niendorf, 1950; Cruttenden and Taylor, 1950; Wolskel *et al*, 1953; Hoynck van Papendrecht and Os, 1962; Kral and Zeman, 1977). We now describe a further patient operated upon in 1978.

CASE REPORT

Clinical details

A nulliparous 47-year-old nurse presented with heavy, irregular and prolonged menstrual periods for ten months. She was taking iron for symptoms of anaemia (haemoglobin 10·8 g/dl). Infertility investigations had been proposed 16 years previously, but declined by the patient. There was no other relevant medical or family history. Physical examination showed her to be fit, but the uterus was bulky and immobile. The lower genital tract and a cervical cytology smear were normal.

At laparotomy the pelvic organs were adherent in an immobile mass. The uterus was bulky, both Fallopian tubes were distended and adherent to each other, to bowel and to the left pelvic sidewall. Both ovaries were deeply buried in the mass. The upper abdomen was normal. The mass was dissected free from bowel and the pelvic wall without undue difficulty and total hysterectomy with bilateral salpingo-oophorectomy performed. She was transfused peroperatively with one litre of blood and made an uneventful postoperative recovery.

When the histopathological findings were known, a chest X-ray and intravenous pyelogram were done and reported as normal. Three early morning urine cultures for *Mycobacterium tuberculosis* were negative, but a Mantoux test was strongly positive. Treatment with rifampicin (600 mg/day) and isoniazid (300 mg/day) was started and she has remained well.

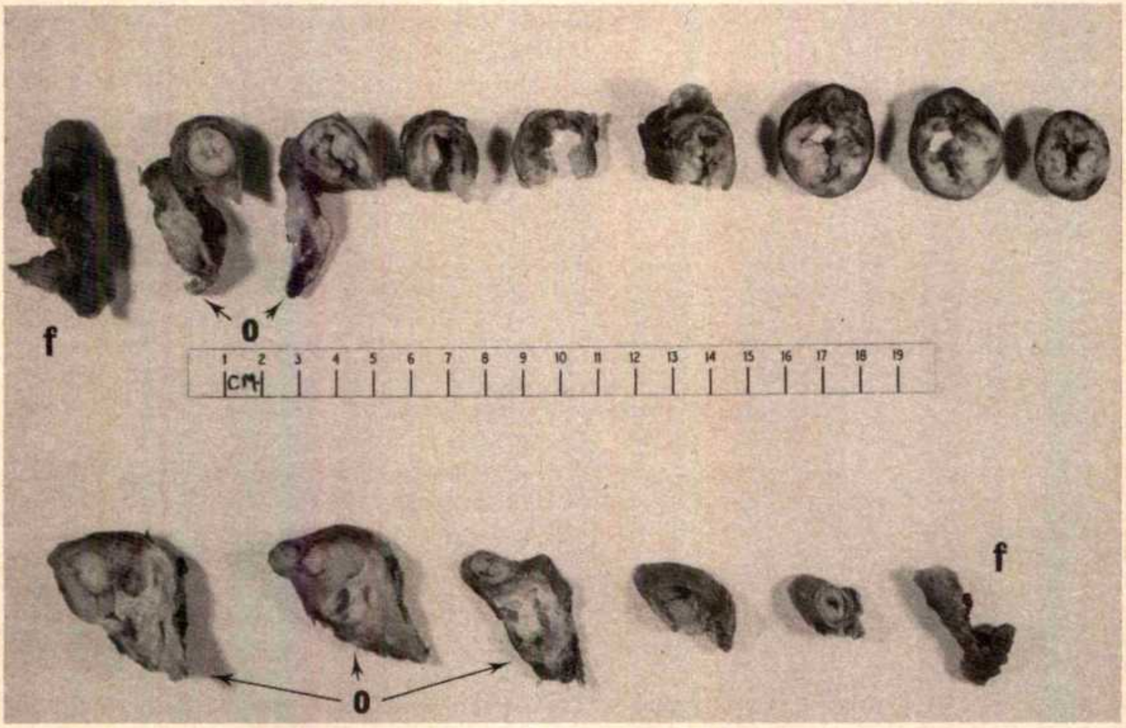

FIG. 1
Macroscopic appearances of both tubes and ovaries after sectioning. Left tube on top. f = fimbrial ends. o = ovaries.

Pathological findings

The uterus and cervix together measured 9·5 × 6·5 × 3·5 cm. The left tube was 8·0 cm long with a maximum diameter of 2·0 cm. It was congested and section revealed a thick mucosa. The left ovary measured 4·0 × 2·0 × 2·0 cm and contained nodules (largest 0·3 cm) on section. The right tube (7·0 cm long) and ovary (5·0 × 3·0 × 3·0 cm) were densely adherent together. The ovary again showed white nodules, and small cysts, on section. Many of these features are seen in the photograph of both tubo-ovarian parts (Fig. 1) of the gross specimen sectioned serially. No significant gross abnormalities were seen in either uterus or cervix.

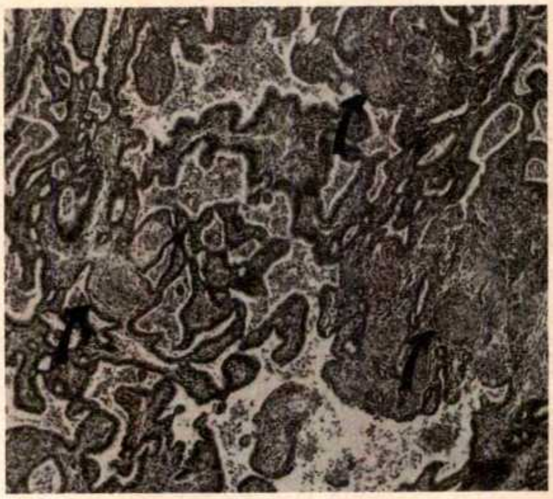

FIG. 2
Hyperplasia of tubal epithelium. Granulomata arrowed. H & E × 40.

Microscopically, representative sections from both tubes and ovaries showed widespread florid hyperplasia of the tubal epithelium (Fig. 2). There were many histocytic granulomata with Langhans' cells scattered through all coats of the tubal wall; and, in fewer numbers, in the ovaries, myometrium and endometrium. There was no caseation. Detailed study of the granulomata revealed a few Schaumann bodies in Langhans' cells, and very scanty indeterminate optically active foreign material in an occasional histocyte or Langhans' cell. No tubercle bacilli were found in numerous Ziehl-Neelson or auramine-rhodamine sections (viewed under ultra-violet light). Gram staining failed to demonstrate other micro-organisms (*Actinomyces* in particular).

In parts of both tubes, hyperplastic epithelium had formed irregular glands (Fig. 3) and numerous areas of solid tumour (Fig. 4). The epithelial cells in these latter areas were markedly dedifferentiated and anisocytic (Fig. 5). Mitotic figures were present in moderate numbers. In some areas the tumour showed a squamoid appearance, and was most prolific in the isthmic areas of both tubes, more so on the left side. The tumour had thinned the tubal wall by expansive growth but, in addition, distinct islets of growth were invading submucosa (Fig. 6). This figure also shows chronic granulomatous inflammatory changes. Involvement of muscle was difficult to determine. Involvement of vessels could not be excluded but no tumour was seen anywhere in the serosa. The tumour did not extend beyond either fimbrial end, nor medial to the interstitial parts, into the uterus.

There were granulomata in the ovaries, myometrium and endometrium, but no new growth or any other pathological feature. The endometrium was in the proliferative phase and the cervix was normal.

DISCUSSION

Two distinct pathological processes were seen in this patient.

An undoubted granulomatous inflammation was found, the commonest cause of which in this country is tuberculosis. Tubercle bacilli were not demonstrated but Novak and Woodruff (1974*a*) comment that a search for the bacillus in histological sections of tuberculous salpingitis is 'classically negative'. Woodruff and Pauerstein (1969*a*) say caseation is rarely seen in tubal tuberculosis, and its absence, as in this case, does not preclude the diagnosis (Burne, 1973*a*). A finding which strongly favours the diagnosis of

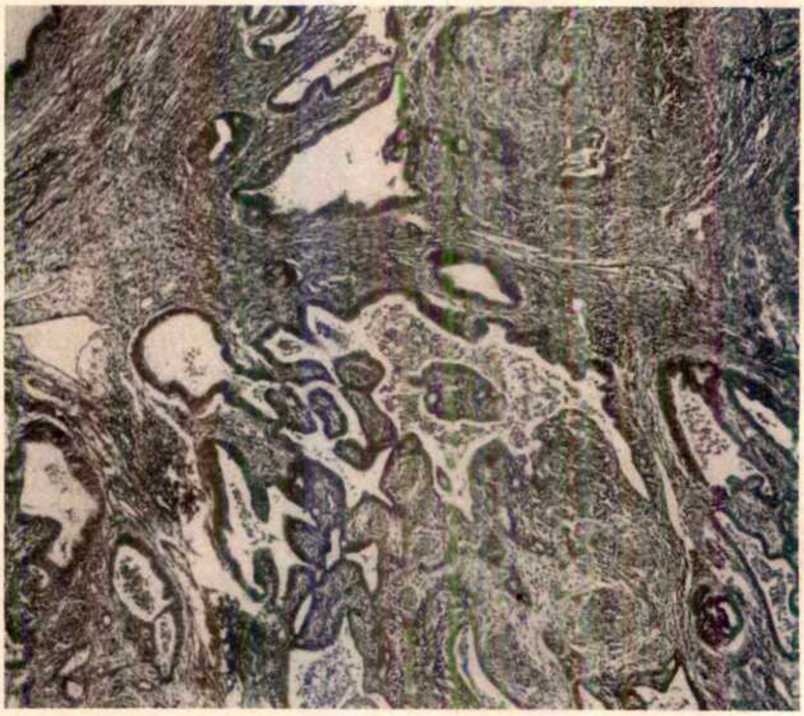

FIG. 3

Irregular glandular areas in tubal epithelium. Much of the stroma shows granulomatous inflammation. H & E × 50.

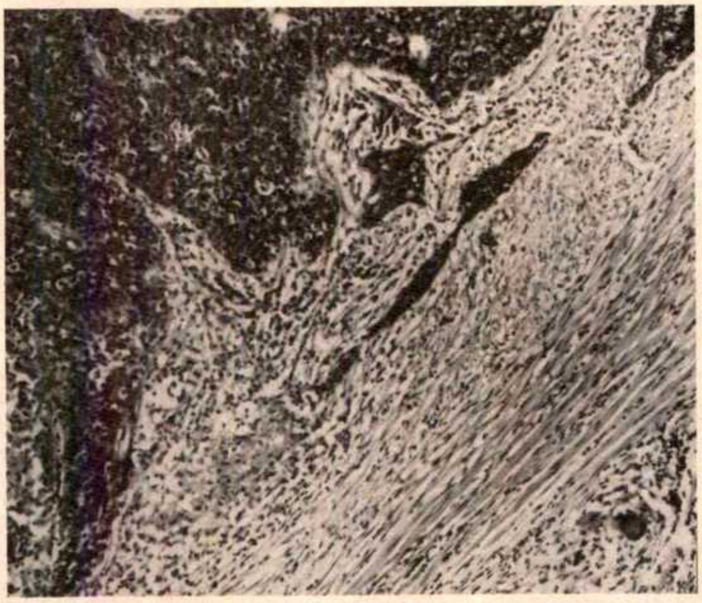

FIG. 4
Solid tumour showing infiltration of submucosa. A granuloma with at least one Langhans cell is evident between muscle fibres, bottom right. H & E × 100.

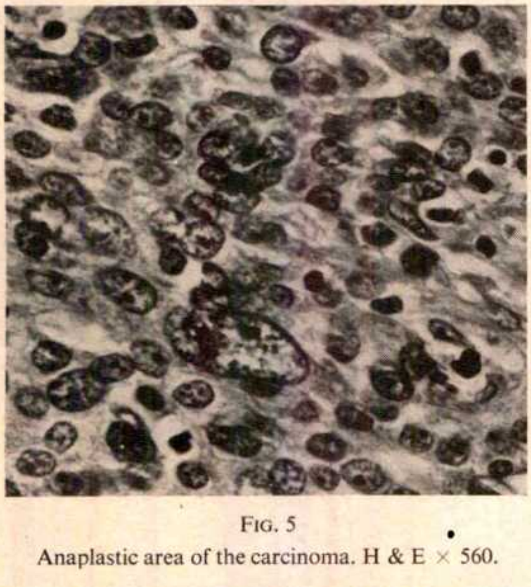

FIG. 5
Anaplastic area of the carcinoma. H & E × 560.

tuberculosis is the presence of Schaumann bodies (Burne, 1953). Other possible causes of granulomata include foreign bodies, animal parasites (schistosomes, pinworms or their eggs), actinomycosis, sarcoidosis and Crohn's disease. Leprosy, lymphogranuloma, granuloma inguinale and syphilis were thought unlikely in this patient. There was no history of abdominopelvic surgery or salpingography to suggest a foreign body reaction. Woodruff and Pauerstein (1969*b*) consider several foreign substances which might be responsible for granulomata in tubes, but Burne (1973*b*) says that he has never seen intratubal granulomata proven due to these causes. The latter also comments that a diagnosis of sarcoidosis is not permissible unless there is evidence of the disease elsewhere, and there was none in this patient. The granulomata seen were too numerous and widespread to be accounted for by a sarcoid reaction to malignant tumour, which is occasionally manifest as one or two granulomata adjacent to new growth. No animal parasites, or actinomycosis, were seen in the numerous sections examined. The patient had no signs of Crohn's disease elsewhere.

The histological findings, her age, occupation as a nurse, history of involuntary infertility, and strongly positive Mantoux test together led to a confident diagnosis of tuberculosis.

Tuberculous salpingitis is known to cause

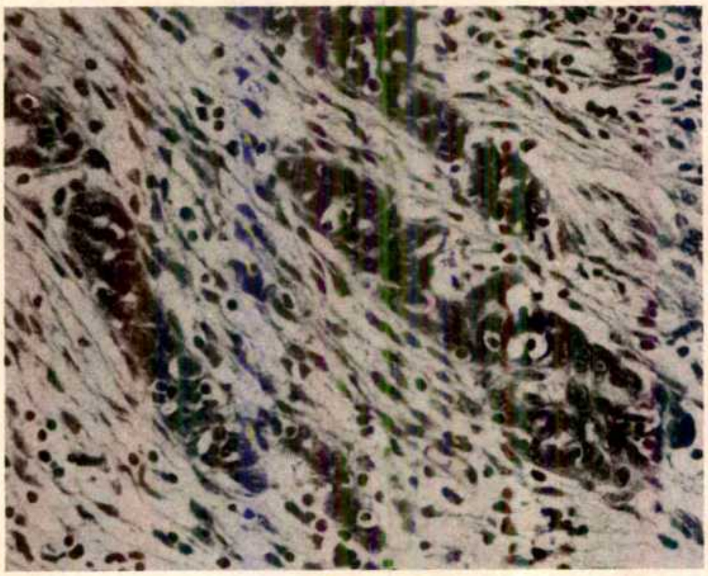

FIG. 6
Carcinoma invading submucosa. H & E × 280.

hyperplasia of the tubal epithelium, which has led to a mistaken diagnosis of cancer (Purflett, 1972). In our patient, the presence of solid and irregular glandular areas of anaplastic structure infiltrating the submucosa (at least) justified the diagnosis of malignancy. Metastatic tumour was thought unlikely because there was no histological evidence of tumour in the ovaries, uterus or cervix and the rest of the peritoneal cavity was noted to be normal at operation. The tumour was bilateral, as it is in between one-third (Burne, 1973*c*) and one-quarter (Sedlis, 1961) of all cases. The latter author quotes a mean age for diagnosis of carcinoma of the tube as 52 years; our patient was 47 years old.

Radiotherapy was felt ill-advised for our patient because of the presence of tuberculosis. Carcinoma of the tube is rare (Woodruff and Pauerstein, 1969*c*). Benedet *et al* (1977) described a 34 per cent five-year survival of 41 cases of carcinoma of the tube diagnosed over 30 years, rising to 73 per cent for cases diagnosed early. Most cases are considered to invade locally and metastasize late and the apparent poor diagnosis may result from late diagnosis rather than a highly malignant nature (Novak and Woodruff, 1974*b*). Our patient's tumours were adequately excised at an early stage and her prognosis should be good.

The question of carcinomatous transformation of tubal epithelium rendered hyperplastic by tuberculous salpingitis has been discussed by Woodruff and Pauerstein (1969*d*), and by Burne (1973*d*). The latter felt inclined to agree with Cruttenden and Taylor (1950) that tuberculous epithelial hyperplasia may predispose to carcinoma, but the evidence for this remains too scanty for statistical assessment.

Tuberculous epithelial hyperplasia is well recognised, and there may be scepticism when a histological diagnosis of carcinoma is suggested. Very careful histopathological assessment of every case of tuberculous salpingitis is prudent, to ensure that cases of treatable malignancy are not missed, or dismissed in error.

ACKNOWLEDGEMENTS

We thank Professor J. S. Scott for permission to report this patient and Professors C. Bird, F. Langley, and R. A. Willis for their advice.

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BOOK REVIEWS

Prenatal Endocrinology and Parturition. Inserm Volume 77. Edited by LISE CÉDARD and CLAUDE SUREAU. Pp v+315 with 76 figs and 64 tables. Inserm, Paris, 1978. Price: 60 Francs.

THIS collection of 23 papers presented in Paris at a Symposium arranged by the French National Institute of Health and Medical Research deals with the important subjects of: (i) fetal maturity and parturition; (ii) biological survey of human pregnancy; (iii) uterine motility; (iv) acute fetal distress and labour, and (v) epidemiology. Under the first heading, fetal and maternal hormones near the end of pregnancy and the hormonal and others factors involved in the onset of labour are considered in papers from France, USA, Great Britain (by Alec Turnbull) and Sweden. The assessment of fetal well-being and anomalies is considered in the second section. Under (iii) and (iv) uterine motility, fetal heart rates, tocography, fetal blood pH and their interrelationships are discussed and the last section deals with prematurity, its prevention and prenatal risks. All the papers are of an extremely high standard, since some of the world's greatest experts were involved in their preparation. The editing is particularly well done as each of those papers delivered in French has an excellent and full English summary and the five papers delivered in English have equally good French summaries. Anyone interested or researching the subjects of hormone involvement in maturity and in the way labour starts will find interesting and valuable material here; and the bibliography at the end of each paper is of great help. It must have been an excellent meeting and the fact that the editors have brought this publication out so quickly is a matter for congratulation.

E. E. Philipp

Nutrition and Metabolism of the Fetus and Infant. Fifth Nutricia Symposium. Edited by H. K. A. VISSER. Pp xvl+419 illustrated. Nartinus Nijhoff, The Hague, The Netherlands, 1979. Price: 110 guilders.

THE Nutricia Symposia are always worth reading. The papers given are topical and often on the fringes of knowledge, the printed discussion is organized and interesting and the whole is beautifully produced well within a year of the meeting; Dr Visser, who had a hand in the editing of all five Nutrition Symposia, has edited this one by himself and is to be congratulated. It is not possible in a short review to be fair to all the participants who contributed 22 papers on the general theme of nutrition in the fetus and the premature and term newborn infant; only to single out some papers which had a personal appeal: an excellent critical review of the roles of insulin and glucogen by Milner, and of fatty acids by Hull; a very useful, if inconclusive, account of the effect of insulin on protein metabolism by Maureen Young; some excellent data on the energy cost of growth in low birth weight infants by Sauer and his colleagues and some exceptional new data on whole body composition of both normally grown and small-for-dates infants by Dr Elsie Widdowson and her colleagues. In comparing this latest symposium with the first one in 1963 there is a trend not merely to the more complex and detailed, which would be expected from the progress of technology, but also to a greater emphasis on animals other than man. Perhaps this is inevitable, but some of the more extreme animal 'models', for example, the growth retarded guinea pig fetus which weighs only 30 per cent of normal, seem very remote from real life. That is a small, personal reservation, and does not detract from the value of a book which any obstetrician or paediatrician interested in fetal growth will want to have.

F. E. Hytten

My Body, My Health—The Concerned Woman's Guide to Gynecology. By F. H. STEWART, F. J. GUEST, G. K. STEWART and R. A. HATCHER. Pp xxi+566 with illustrations. John Wiley and Sons, Chichester, 1979. Price: £9.00 Clinician's edition. £4.00 Paperback ed excluding Patient Education chapters.

THIS is an excellent book for the gynaecologist to recommend to women patients in Britain, as the slight American bias in respect of explanations and consent does not detract from its value. It contains easily readable and comprehenisve information on reproductive physiology, including adolescence, contraception and sterilization, venereal disease and gynaecological problems, with the surprising omission of utero-vaginal prolapse. It will serve to supplement and reinforce the teacher/student aspect which is so essentially a part of the modern doctor/patient relationship. The approach is warm and it presents a philosophy on health problems which neither mystifies nor exults the medical input. It does not view the clinician as an enemy. The absence of paternalism will enhance its value. Any tendency to increase anxiety in some will be offset by considerable reassurance given to the majority, as the presentation is balanced and sensible. The hardback edition contains two chapters on advice to clinicians on patient education and informed consent which are not included in the paperback edition. Line diagrams and general illustrations are excellent, and the presentation is of good quality and appealing to the eye. I recommend this book wholeheartedly.

H. A. Brant

Prenatal Pathology Fetal Medicine. By T. V. N. PERSAUD, with the collaboration of M. RAY and H. RIGATTO. Pp v+199 with 76 figs and 31 tables. Charles C. Thomas, Springfield, 1979.

MUCH has been written about the clinical and physiological aspects of intrauterine life but relatively little about true pathology. This small book has an attractive title which invites all those interested in perinatal medicine to read it. The author summarises the objectives of his book well when he writes 'This book cannot and does not attempt to provide full explanation of all aspects of fetology. However, an attempt has been made to bridge the gaps between the medical disciplines concerned with the fetus . . .'. The subjects covered range from the pathophysiology of early development to a chapter on common neonatal problems. It is clear, even from the chapter headings, that the real interest of Dr Persaud is the aetiology of congenital defects. His descriptions of early development and its regulation admirably summarise a difficult subject for most readers. The chapter on chromosomes is a particular example of his lucid style. Whereas the section devoted to the antenatal diagnosis of genetic diseases is confused by numerous tables from different studies which describe the results of tests on amniotic fluid and the outcome of the pregnancy without attempting to summarise the role of amniocentesis in reducing the incidence of congenital malformations. In addition, one suspects that the publishers have pressed the author to include a clinical component to give the book wider appeal. There is no other explanation for the last chapter, which is not only weak but out of place. It is the attempt 'to bridge the gaps between the medical disciplines' that has led to the extreme unevenness of the book. There is no doubt that clinicians need to know a lot more about early development generally if the number of babies born with congenital defects is to be reduced. However, it is the lack of information on the subject rather than its application that needs to be remedied. Anyone who comes across this book will enjoy the chapter on chromosomes and will find the chapter on antenatal diagnosis useful for reference. The book, as a whole, cannot be strongly recommended to obstetricians as essential reading.

R. W. Beard

Die Laparoskopie in der Gynakologie, Chirurgie und Padiatrie. Lehrbuch und Atlas. By H. FRANGENHEIM, with a contribution entitled Hysteroskopie by H.-J. LINDEMANN. Pp ix+214 with 164 illustrations (92 of them multi-coloured). Georg Thieme, Stuttgart, 1977. Price: DM 98.

IN the last 15 years laparoscopy has profoundly affected gynaecological practice. There can be only few gynaecologists left with sufficient confidence in their diagnostic ability to be able to dispense with the laparoscope. For the rest it offers a way of achieving rapid and exact diagnoses, shortened hospitalization following operative procedures in some patients and avoidance of unnecessary laparotomy in others. Nobody has made a greater contribution to the development of the techniques and instruments used in laparoscopy than Professor Hans Frangenheim, working not in a University centre, but in the small and lovely town of Konstanz. This new and revised edition of his well known monograph is beautifully written, illustrated and produced. There are detailed chapters on instrumentation, techniques, diagnostic and operative uses of the laparoscope and complications. These are followed by shorter sections on laparoscopy in general surgery and paediatric practice; fetoscopy; the training of junior staff, and the author's general philosophy on the role of laparoscopy in gynaecological practice. A succinct chapter by Professor Lindeman on hysteroscopy completes the book. The bibliography is particularly satisfying with over 900 references including very many from the British and American literature. This book embodies the wisdom and experience of a great clinician. It should be on the shelves of all medical libraries and all progressive gynaecologists.

H. Reiss

Gynecological Cytopathology. Edited by M. J. AYALA and F. N. ORTIZ. Pp xvi+285 with illustrations, figures and tables. The C. V. Mosby Company, USA, 1979.

THE authors of this book aim to correlate cytology and histology, and to present new contributions. There are chapters on all aspects of gynaecological cytology, the urocytogram, ascitic fluid and the breast. The writer of the foreword hopes it will be of use to English-speaking workers as it represents the work done by the best Spanish cytologists. Unfortunately the translation tends to frustrate the authors' intentions. Inappropriate words are used, such as 'beehive' when 'honeycomb' pattern is intended, and sometimes this makes whole phrases unintelligible: the section on Cytological Control of Pregnancy shows smears from patients with 'a live check fetus' and a 'still sour fetus'. Misprints are too frequent and some of the photomicrographs, particularly the black and white histological ones, lack definition. If this could be corrected, a particularly useful part of this atlas would be the section on benign and malignant breast lesions.

Avril E. Paintin

Placental Transfer. Edited by G. V. P. CHAMBERLAIN and A. W. WILKINSON. Pp 212 with figures and tables. Pitman Medical, Kent, 1979. Price: £15.00.

UNTIL recently, as stated in the foreword, most tests of placental function have measured endocrine metabolism rather than the transfer capacity of the placenta. This volume (with 17 contributors—all, bar one, from the UK) contains information about the transfer of many substances required by the fetus and shows the effects of diminished placental transfer in different species. The first two chapters deal with the anatomy of placental transfer and the correlation between placental structure and transfer function. The following three chapters discuss blood flow—maternal, fetal and placental. Following a chapter devoted to the physiological adaptation to diminished placental transfer, more than one third of the text (6 chapters) is used to review transfer of specific substances—water, carbohydrates, amino acids, fatty acids, respiratory gases and to consider drug transfer principally in relation to drugs used in relation to drugs used in labour. Only the last twenty or so pages of the book have a really human and clinical flavour considering the clinical assessment of placental transfer and the effects of hypertension and diabetes. This volume is by no means light reading but it presents an excellent collection of papers with good bibliography and should provide a valuable reference source for obstetricians, perinatologists, physiologists, pathologists, and all those seeking guidance in the understanding of the highly complicated mechanisms, controls and vagaries of placental transfer.

D. V. I. Fairweather

BOOKS RECEIVED BUT NOT REVIEWED

Handbook of Obstetrics and Gynaecology. Edited by BARRY G. WREN. Pp x+454 with 116 illustrations. Baillière Tindall, London, 1979. Price: £5.00 (limp).

Human Reproduction: Physiology and Pathophysiology. Edited by R. W. HUFF and C. J. PAUERSTEIN. Pp viii+497 with figures and tables. John Wiley & Sons, Chichester, 1979. Price: £9.00.

Life and Death Before Birth. A Working Party Report prepared for and approved by The Council for Science and Society. Pp 64 with 3 figs and 5 tables. Council for Science and Society, 3/4 St Andrew's Hill, London, EC4 V5BY, 1979. Price: £1.50.

Journal of Developmental Physiology—Volume 1, No. 1, February 1979. Bi-monthly. Edited by COLIN T. JONES. Pp 103+vi. Blackwell Scientific Publications, Oxford, 1979. Subscription rates: £33 per annum (UK); £39.50 per annum (overseas).

The Quality of Life—The Peckham Approach to Human Ethology. By I. H. PEARSE. Pp xvi+194 with figures and tables. Scottish Academic Press, Edinburgh, 1979. Price: £6.50.

Surgical Review 1. Edited by J. S. P. LUMLEY and J. L. CRAVEN. Pp vii+407 with illustrations. Pitman Medical Ltd, Kent, 1979. Price: £9.95.

Antepartum Cardiotocografie in de Verloskundige Praktijk. (The use of antepartum cardiotocography in clinical practice). By J. B. TRIMBOS. Pp 254 illustrated. Proefschrift (Thesis), Leiden, The Netherlands, 1979.

Traditional Birth Attendants, WHO Offset Publication No. 4. Pp 109 illustrated. WHO, Geneva, 1979. Price: Sw. fr. 12.

Service-oriented Research in Adolescent Fertility. Report on a WHO Meeting. (Euro Reports and Studies No. 1). Pp 37 with figures and tables. Regional Office for Europe. WHO, Copenhagen, 1979. Price: Sw. fr. 5.

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